Dietary intervention with serum-derived bovine immunoglobulins protects barrier function in a mouse model of colitis

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First published April 16, 2015; doi:10.1152/ajpgi.00378.2014.

In maintaining correct barrier function, since mice lacking mdr1a gene (KO) were fed diets supplemented with either SBI (2% wt/wt) or milk proteins (control diet), from day 21 (weaning) until day 56. The epithelial permeability of distal colon crypts was measured by confocal microscopy using a fluorescent marker. The expression of junctional epithelial E-cadherin and β-catenin proteins were determined by Western blot and zonula occludens-1 (ZO-1) by immunofluorescence. Mucins (MUC1, MUC2, MUC4), TFF3, cytokines (TNF-α, IFN-γ), and inducible nitric oxide synthase RNA expression were quantified by real-time PCR. SBI blocked the increase in colon crypt permeability and partially prevented the reduction in E-cadherin and ZO-1 expression that characterizes the KO mouse model (both P < 0.05). SBI inclusion also reduced the mucosal expression of the inflammatory markers TNF-α, IFN-γ, and inducible nitric oxide synthase (all P < 0.005). The number of goblet cells in the colon of KO mice was low and correlated well with MUC2 and TFF3 expression (P < 0.001), whereas dietary supplementation with SBI attenuated these effects (all P < 0.05). In short, dietary SBI ameliorated colonic barrier alterations and reduced the expression of mucosal inflammatory markers in a genetic model of IBD.

The incidence of chronic inflammatory bowel diseases (IBD) has increased over recent decades, particularly in developed countries (22). No etiopathogenesis of IBD has been clearly established, but it has been hypothesized that intestinal barrier dysfunction, with increased permeability, is a major part of the process (35). In animal models of intestinal inflammation, restoring intestinal barrier function has been shown to ameliorate the development of inflammation (3, 25). Another characteristic of IBD is a reduction both in the number of goblet cells and in mucin secretion from the colon mucosa, which impairs its protective functions (10). Trefoil factors also play a key role in maintaining correct barrier function, since mice lacking trefoil factor-3 (TFF3) are more susceptible to DSS-induced colitis (20).

IBD therapy depends on the use of immunosuppressive drugs or biological agents, including anti-TNF-α antibodies. However, a large proportion of patients either are nonresponsive or develop side effects that may reduce their quality of life (38). Nutritional intervention is an important adjunctive therapy for patients with IBD (26) because it can improve the protective functions of the gastrointestinal mucosa and reduce mucosal dysbiosis, thus regulating the immune response.

Serum-derived bovine immunoglobulin (SBI) is a specially formulated medical food supplement that provides specific nutritional support for the clinical dietary management of intestinal pathologies (33). Partial replacement of common dietary protein sources by immunoglobulins from animal plasma has previously been shown to modulate inflammatory response in the gut (4, 24). In an experimental model of acute intestinal inflammation induced by the administration of Staphylococcus aureus enterotoxin B (SEB), the dietary inclusion of plasma proteins attenuated the effects of SEB on the expression of tight junction and adherens junction proteins, which regulate epithelial permeability (25, 27). These observations are consistent with the view that the dietary inclusion of proteins from animal plasma can decrease the production of cytokines in the inflamed intestinal mucosa (29).

In view of these effects related to the prevention of mucosal inflammation, and since IBD is characterized by alterations of intestinal permeability, we aimed to determine whether SBI can modulate intestinal barrier function in mice with a genetic predisposition toward IBD. We chose the mdr1a−/− mouse model of spontaneous colitis because it suffers from barrier alterations, anomalous immune responses, and bacterial colonization, all important factors associated with human intestinal inflammation (34, 43). The mdr1a gene encodes P-glycoprotein 170 (P-gp), a transport protein involved in the removal of drugs and xenobiotic substances from cells. In mice lacking P-gp, exposure to conventional bacteria induces progressive and severe colonic inflammation and colitis (5, 34). In humans, decreased P-gp expression has been associated with ulcerative colitis, which further supports the clinical relevance of the mdr1a−/− mouse model to our study (36).

**MATERIALS AND METHODS**

***Animals and experimental design.*** Mdr1a−/− mice (FVB.129P2-Abcb1atm1Bbn7; KO) and the corresponding FVB wild-type mice (WT) were supplied by Taconic (Germantown, NY). From these animals, we generated a stable colony in the specific pathogen-free (SPF) area of the Animal Experimentation Service of the Barcelona.
Science Park (BSP), University of Barcelona. Animals were kept under stable temperature and humidity conditions, with a 12:12-h light-dark cycle. All protocols used in this study were approved by the Ethics Committee for Animal Experimentation of the BSP. The animals were weaned at day 21 of age and then consumed the experimental diets until the end of the study. The animals were fed a control diet or a diet supplemented with SBI, a functional protein supplement composed of >50% IgG as well as other proteins and peptides which reflect the composition of plasma. The experimental diets were prepared and irradiated by Harlan Ibérica (Barcelona, Spain) and the composition is shown in Table 1. The experimental groups used throughout the study were WT (WT mice fed control diet), KO (KO mice fed control diet), SBI (WT mice fed SBI diet), and KO-SBI (KO mice fed the SBI diet).

In preliminary experiments, it was noted that 8- to 10-wk-old mice kept in SPF conditions showed very mild signs of colitis, but when transferred to the conventional area of the animal facility the mice excreted soft feces and, in some cases, experienced diarrhea. From these observations we decided to maintain the mice in the SPF area until day 28 of age, and then we transferred them to a conventional housing area until day 56, when they were killed by anesthesia overdose.

Disease activity index. With this protocol, the KO mice developed clinical and histological signs of colitis that were scored by the disease activity index (DAI). The score was assigned to each mouse by the personnel of the Animal Experimentation Service of the BSP. The parameters analyzed were weight loss (score: 0, none; 1, 1–5%; 2, 5–10%), stool consistency (score: 0, formed; 1 soft; 2 watery stool), and bleeding (score: 0, normal; 1, blood occult in feces; 2, bloody).

Morphological study. Samples of the descending colon were washed with PBS and fixed for 24 h with 4% paraformaldehyde, dehydrated in graded ethanol, and embedded in paraffin. Hematoxylin-eosin and periodic acid Schiff (PAS) staining were performed according to standard protocols. Histopathological analysis was performed by the Pathological Anatomy Department of the Vall d’Hebron Hospital (Barcelona, Spain), under blind conditions. The degree of inflammation of the colon was graded semiquantitatively from 0 to 14, according to the previously defined criteria of Angulo et al. (1), which take into account mucus depletion, lamina propria and transmural cellular infiltration, cryptitis, and crypt abscesses. Goblet cells were quantified in sections stained with PAS reagents, observed in blind conditions under an optic microscope BX41 (Olympus, Münster, Germany) and counted by use of ImageJ software (http://imagej.nih.gov/ij/).

Epithelial fluorescent dextran permeability. The procedures were performed as described previously (23). Briefly, the mucosa of the descending colon was scrapped and kept for 15 min in a petri dish containing carboxgenated Earl’s solution at 37°C to stabilize the sample.

Cryopreservation of dextran was monitored by the rate of escape of fluorescein isothiocyanate (FITC)-labeled dextran (FITC-dextran; molecular weight 4,000; Sigma-Aldrich, St. Louis, MO) into the crypt lumen and the pericryptal space at 37°C. Crypt luminal and pericryptal concentration of FITC-dextran was estimated by monitoring the ratio of fluorescence intensity of each zone. Tissue samples were incubated for 15 min and confocal images were taken every 3 min with a CLSM SPII confocal microscope (Leica Microsystems, Heidelberg, Germany). Two fields were captured per tissue per animal. The image was analyzed as previously described (23) and fluorescence in the crypt lumen and in the pericryptal sheath was quantified by using the ImageJ software. Ten crosps were analyzed per field (20 crosps/animal).

Immunohistochemistry of ZO-1. Paraffin sections (5 μm) of the descending colon were used for the immunolocalization of zonula occludens-1 (ZO-1), as described previously (27). Sections were permeabilized with Triton X-100 (Sigma) 0.1% and blocked with 1% BSA (vol/vol; Sigma) at room temperature for 30 min. The primary antibody, a rabbit polyclonal anti-ZO-1 (1/50, Zymed, Carlsbad, CA), was incubated overnight at 4°C in a humidified chamber. Sections were washed with PBS and incubated with the Alexa Fluor 532-conjugated goat anti-rabbit antibody (1/200, Molecular Probes, Eugene, OR). Negative controls were performed without the primary antibodies. Samples were stored at 4°C until observation with a TCS SPE confocal microscope (Leica Microsystems). The captured images were analyzed with the ImageJ software.

Western blot analysis. Western blot procedures were performed as previously described (21). The protein concentration was determined by the Bradford method (Bio-Rad, Munich, Germany). Blots were incubated overnight at 4°C with agitation with the following primary antibodies: rabbit polyclonal anti-β-catenin at a dilution of 1/2,000 (NeoMarkers, Fremont, CA), rabbit polyclonal anti-E-cadherin at a dilution of 1:200 (Santa Cruz Biotechnology, Dallas, TX) and mouse monoclonal anti-GAPDH at a dilution of 1:10,000 (Sigma). The blots were developed by using WesternDot 625 Western blot kits (Life Technologies, Paisley, UK) and quantified with ImageJ gel analyzer software.

Real-time PCR analysis. RNA extraction and reverse transcription were carried out as described previously (18). Total RNA was retrotranscribed by use of an iScript cDNA Synthesis Kit (Bio-Rad). For RT-PCR determinations, a template of cDNA was incubated in a 20-μl reaction containing 0.3 μmol/l of each primer and SsoAdvanced Universal SYBR Green Supermix (Bio-Rad). The primers used to detect inducible nitric oxide synthase (iNOS), TNF-α, IFN-γ, and GAPDH are previously described elsewhere (18). The primers used to detect MUC1, MUC2, MUC4, and TFF3 were as follows: MUC1 forward AGTTTACGGTGACGGCTTGGTTG and reverse AC-CCTCCGGAAAAACCAAGTGT; MUC2 forward TGGGCTCTGCA-GAGTTGGTTG and reverse CGGACCGTTGGTTGAGGGC; MUC4 forward GGCCTCGTGGAGCTTGTGT and reverse AGCTTCCCGAGATTG and reverse CGGACCGTTGGTTGAGGGC; TFF3 forward GCCCTCTG GCTATCGTGTGT and reverse CTTGGAGACAGGCCAAGCT; GAPDH forward GGCCTCGTGGAGCTTGTGT and reverse AGCTTCCCGAGATTG and reverse CGGACCGTTGGTTGAGGGC.

Western blot analysis was confirmed by melt-curve analysis. RT-PCR determinations were performed on a MiniOpticon Real-Time PCR System (Bio-Rad). Samples were tested in duplicate and the average values were used for the quantification, which was carried out by the 2-ΔΔCT method (17). Product fidelity was confirmed by melt-curve analysis.

Statistical analysis. The data from the experiments are presented as means ± SE, except for the DAI score and histopathological index (HPI), which are expressed as medians. Mean values of normally distributed data were compared by one-way ANOVA followed by Scheffé’s post hoc test. Median values for nonparametric data were compared by the Kruskal-Wallis test. Correlation between the presence of colon goblet cells and MUC2 RNA expression was analyzed by Pearson’s test. All the statistical tests were performed with SPSS-17.0 software (IBM, Armonk, NY). Differences were considered significant at P < 0.05.

Table 1. Composition of the experimental diets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Control, g/kg</th>
<th>SBI Diet, g/kg</th>
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<tr>
<td>SBI*</td>
<td>20</td>
<td>254.8</td>
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<tr>
<td>Corn starch</td>
<td>199.3</td>
<td>254.8</td>
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<td>Skim milk</td>
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<td>Sugar</td>
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<td>Soybean oil</td>
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<td>70</td>
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<td>50</td>
</tr>
<tr>
<td>AIN-93 GM†</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>AIN-93 VX†</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>dl-Methionine</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Choline bitartrate</td>
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<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>1,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

*Serum-derived bovine immunoglobulin (SBI) contains >90% protein, over 50% of which is IgG. Manufactured according to FDA bulk pharmaceutical ingredient standards by EnteraHealth (Cary, NC) under the commercial name EnteraGam. Provided by Harlan Ibérica (Barcelona, Spain).
RESULTS

Dietary SBI improved some inflammatory markers in the colon of mdr1a−/− mice. The results indicate that 8-wk-old KO mice have clinical, histological, and biochemical signs of intestinal deterioration. Quantification of clinical signs using the DAI at the end of the experimental period (day 56 of age) showed that KO animals had a score nearly three times that of WT mice (P < 0.05; Fig. 1A). The dietary inclusion of SBI in the KO animals trended toward an effect on DAI (P < 0.07). Figure 1C shows that the morphology of the colon of KO mice suffered massive enlargement and an increase in wall thickness that doubled that of WT mice. Results in the KO-SBI group showed that SBI supplementation, while not affecting the diameter of the colon, reduced the degree of mucosal distension that characterizes the KO animals.

KO mice had an HPI of 10.6, which is severalfold higher than that of the WT mice (P < 0.001; Fig. 1B), and this was not significantly modified by dietary inclusion of SBI (P < 0.11). Separate analysis of the variables contributing to the HPI showed that four of them (the presence of crypt abscesses, cryptitis, and both lamina propria and transmural infiltration) were not affected by SBI; however, there was a 33% reduction in mucus depletion (KO score, 2.39; KO-SBI score, 1.54; P < 0.01).

In the colon mucosa of KO mice, the expression of TNF-α was increased 20-fold and that of IFN-γ 70-fold, compared with WT animals (both P < 0.001; Fig. 2, A and B); both were reduced by the dietary inclusion of SBI (both P < 0.005). The expression of iNOS was also markedly increased in KO mice (P < 0.001) and significantly reduced by SBI supplementation (P < 0.001; Fig. 2C).

Dietary SBI improved the impaired epithelial barrier function in mdr1a−/− mice. The analysis of FITC-dextran accumulation in the pericryptal sheath of the distal colon showed that the epithelial permeability of KO mice was threefold higher than that of WT animals (P < 0.001; Fig. 3, A and B). Dietary SBI greatly reduced the colon permeability of KO mice (P < 0.001). The increased crypt permeability observed in KO mice was correlated with reduced expression of the adherens junction proteins E-cadherin (P < 0.05; Fig. 3, C and D) and β-catenin (P < 0.001, Fig. 3, C and E), and the tight junction protein ZO-1 (P < 0.05; Fig. 3, F and G). The dietary inclusion of SBI partially prevented the effects on E-cadherin (P < 0.001).
and ZO-1 ($P < 0.05$) but did not affect the expression of $\beta$-catenin.

**Dietary SBI ameliorated goblet cell depletion and the reduction in mucin expression observed in mdr1a$^{-/-}$ mice.** Consistent with the effects on mucus depletion mentioned above, the KO mice showed a 30% reduction in the number of goblet cells with respect to the WT mice ($P < 0.05$; Fig. 4, A and B). Dietary supplementation with SBI increased the number of goblet cells in the descending colon in both WT and KO mice (both $P < 0.05$).

The colonic mucosa of the KO mice had increased MUC1 (6-fold) and MUC4 (3-fold) RNA expression (Fig. 4, C and E, respectively; both $P < 0.01$) and these effects were reduced by the dietary inclusion of SBI ($P < 0.01$). Furthermore, the colon of the KO mice showed a marked reduction in RNA expression of MUC2 and TFF3 (both $P < 0.05$; Fig. 4, D and F). SBI attenuated the colitis effect on MUC2 and completely prevented the effect on TFF3 RNA expression ($P < 0.05$, both variables). There was a strong and positive correlation between the number of goblet cells in colon mucosa and MUC2 expression (Pearson’s correlation was 0.994, $P < 0.001$).

**DISCUSSION**

The aim of this study was to evaluate the effects of dietary supplementation with SBI on the evolution of IBD in a mouse...
model of spontaneous colitis. In our housing conditions, mice lacking P-gp showed disease indicators and histological changes fully compatible with the colitis syndrome, already at week 8 of age. The early onset of clinical signs (e.g., enlarged colon and a reduced number of goblet cells) confirms the previous observations of Resta-Lenert et al. (34) in the same animal model. Other histological alterations reported here in the 8-wk-old KO mice are analogous to those described in 6- to 11-wk-old (5) and 12-wk-old animals (34). An impaired intestinal barrier allows unprocessed luminal antigens to interact with the mucosal immune system, thereby leading to an abnormal immune response (40). The situation is worsened when there is low or no expression of P-gp, because this increases the risk of developing colitis (34, 36). Consequently, restoration of intestinal integrity is a main objective for therapeutic strategies.

The present study shows that SBI inclusion reduces the mucosal expression of inflammatory cytokines and prevents the increase in crypt permeability associated to the colitis syndrome. It also shows that dietary SBI has borderline effects on clinical signs of colitis such as weight loss, stool consistency, and bleeding, or on variables that constitute the histological index. It seems, therefore, that the effects at molecular and cellular levels are paralleled by changes in some clinical and histopathological indicators, though differing in the magnitude of the response. Discrepancies between clinical evaluation and cytokine expression have also been reported in pharmacological studies done in animal models of intestinal inflammation and IBD patients (2, 5). The limited effects of SBI in preventing the clinical manifestations of colitis can be the consequence of the lack P-gp expression that results in continuous exposure of the mucosa to a variety of luminal antigens and toxins causing permanent mucosal alterations that cannot be counteracted by the SBI-dependent changes in cytokine profile.

The permeability across the colon crypt epithelium of the KO mice was three times higher than in WT animals, and it was inversely correlated with the expression of E-cadherin and ZO-1, consistent with the alterations in tight junction structure and in epithelial permeability observed in IBD (8), as well as in a model of intestinal inflammation (27). Dietary intervention prevented 80% of the change in crypt permeability and the effects on E-cadherin and ZO-1 expression by 30–40%, a pattern similar to that observed in previous studies of the SEB model (27). The colon mucosa of the KO mice also showed increased expression of TNF-α and IFN-γ RNA, which are usually produced during mucosal inflammation (29), and iNOS expression, thereby confirming previous results with this model (34). Proinflammatory cytokines can disassemble the tight junction proteins, resulting in a further increase of epithelial permeability (41), which triggers and perpetuates local inflammation in IBD (16). Furthermore, both TNF-α and IFN-γ induce iNOS expression, which also has deleterious effects on intestinal integrity (15). Dietary SBI reduced the increase in the expression of cytokines and iNOS, suggesting that they mediate the changes in permeability during the development of colitis.

The colonic barrier is constituted not only of the colon epithelium but also of the mucus layer, involving cell surface mucins, such as MUC1 and MUC4, and secreted mucins, such as MUC2 (37). Patients with IBD often show altered mucin expression, maturation, and secretion (7). In addition to mucins, goblet cells synthesize trefoil factors, which are secretory proteins that stabilize the mucus layer (39) and facilitate intestinal epithelial restitution (14). The number of goblet cells that synthesize both mucins and intestinal trefoil factors (e.g., TFF3) is reduced in active IBD, and the mucus layer is consequently thinner (37). Alterations in the mucus layer due to a lack of MUC2 production result in enhanced bacterial adhesion to the surface epithelium, increased intestinal perme-
ability, and increased susceptibility to colitis (32). The KO mice showed a marked reduction in both MUC2 and TFF3 RNA expression, as well as in the number of goblet cells in the colon, whereas dietary inclusion of SBI mitigated these effects. The surface mucins MUC1 and MUC4 are membrane-bound mucins involved in cell signaling, adhesion, growth, and immune modulation (7). Furthermore, MUC1 has the capability to recruit T cells to the inflamed colon (13) and also contributes to the disruption of tight junctions (37). The KO mice showed a notable increase in both MUC1 and MUC4 RNA expression, consistent with results obtained in humans (12), whereas the dietary SBI attenuated these effects.

There is evidence that the effects of SBI on mucus and mucin secretion involve interactions of dietary Ig with the microbiome; for example, plasma supplements can restore the secretion of antimicrobial peptides in inflamed animals (30), they can bind and neutralize endotoxin and other microbial components (33), and they can also affect the microbiota profile in both humans (4) and rats (19). These changes can modify the cross talk between the host and the microbiota and lead to an improvement in permeability, inflammation, and the function of the mucus layer.

In addition to its effects on barrier functions, dietary supplementation with plasma proteins attenuates intestinal inflammation in farm animals and in experimental animal models of inflammation. This therapeutic effect is fully manifested when experimental animals are exposed to bacteria and bacterial toxins (28). Immunoglobulin concentrates from animal plasma can reduce both the expression of mucosal proinflammatory cytokines and the activation of Th subsets in lamina propria and epithelium (31). At the same time they can enhance the expression of anti-inflammatory cytokines (29), thereby contributing to the restoration of intestinal homeostasis. Therefore, SBI supplementation may act at two levels with considerable overlapping: on the one hand, it partially restores the barrier properties at mucosal and epithelial levels, hence reducing exposure to food and bacterial antigens; on the other, it reduces the magnitude of the immune response and the production of proinflammatory cytokines, which, all together, affect permeability.

The conventional treatment options for IBD are corticosteroids and immunosuppressive agents to attenuate the inflammatory process. However, corticosteroids have proved ineffective in a large subgroup of patients; population-based studies have shown that a significant fraction of Crohn’s disease patients treated with corticoids develop steroid dependency or even steroid-refractory illness (9). In view of the moderate therapeutic effect of these drugs and their possible association with severe side effects, there is a clear need for more effective therapies.

The lack of toxic side effects (6) and its effectiveness in restoring the barrier properties of the colonic epithelium suggest that SBI has a potential as a nutritional therapy adjunctive to conventional treatments to help manage patients with IBD.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the technical assistance of Toméu Fernández and Maryna Kurylenko.

GRANTS

This work has been supported by grant TRA2009 0317, Ministerio de Ciencia e Innovación, Spain and grant RDITCRD07-1-0008, CIDEM, Generalitat de Catalunya. The research group is also supported by grant 2009SGR0471 for Consolidated Research Groups, Generalitat de Catalunya, Spain.

DISCLOSURES

A. Pérez-Bosque, L. Miró, M. Maijó, and M. Moretò declare that they have no conflict of interest; J. Polo is employed by APC Europe S.A. (Granollers, Spain); I. Campbell, L. Russell, J. Crenshaw are employed by APC Inc. (Ankeny, IA); E. Weaver is employed by EnteraHealth (Cary, NC).

AUTHOR CONTRIBUTIONS


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12. Hoebler C, Gaudier E, De Coppet P, Rival M, Cherbut C. MUC genes are differently expressed during onset and maintenance of inflammation in both humans (4) and rats (19). These changes can modify the cross talk between the host and the microbiota and lead to an improvement in permeability, inflammation, and the function of the mucus layer.

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ORAL IMMUNOGLOBULINS PROTECT COLON BARRIER FUNCTION


