Role of the High Affinity Immunoglobulin E Receptor in Bacterial Translocation and Intestinal Inflammation

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Abstract

A role for immunoglobulin E and its high affinity receptor (FceRI) in the control of bacterial pathogenicity and intestinal inflammation has been suggested, but relevant animal models are lacking. Here we compare transgenic mice expressing a humanized FceRI (hFceRI), with a cell distribution similar to that in humans, to FceRI-deficient animals. In hFceRI transgenic mice, levels of colonic interleukin 4 were higher, the composition of fecal flora was greatly modified, and bacterial translocation towards mesenteric lymph nodes was increased. In hFceRI transgenic mice, 2,4,6-tri-nitrobenzenesulfonic acid (TNBS)-induced colitis was also more pronounced, whereas FceRI-deficient animals were protected from colitis, demonstrating that FceRI can affect the onset of intestinal inflammation.

Key words: immunoglobulin E receptor • bacterial translocation • intestinal permeability • inflammatory bowel disease • colitis

Introduction

IgE is known to induce inflammatory processes such as immediate hypersensitivity reactions (allergy, asthma, anaphylaxis, etc.) through interaction with its high affinity receptor, FceRI (1). Upon receptor aggregation with IgE and multivalent antigen, cells release inflammatory mediators, whether preformed, like histamine, or newly synthesized, like leukotrienes. In mice, FceRI is expressed only on mast cells and basophils, whereas in humans, it is additionally expressed on monocytes, Langerhans cells, eosinophils, and platelets (1). To obtain the most suitable animal model for the study of IgE-mediated diseases, we first generated transgenic (Tg) mice expressing the human FceRIα (hFceRIα) chain under the control of its own promoter region (2).

Those hFceRIα Tg animals (bred in an FceRI-deficient background), express a “humanized” receptor, with the same cellular distribution as found in humans (3). This receptor is able to bind human or murine IgE and to restore IgE-mediated anaphylaxis in FceRI-deficient (FceRIα−/−) mice (2, 4).

In chronic inflammatory bowel disease (IBD), intestinal lesions are considered as the consequence of a dysfunction of the mucosal immune system. Genetic and environmental factors have also been associated to the onset of the disease. Infectious agents such as Mycobacterium paratuberculosis, measles virus, and Listeria monocytogenes were once suspected as causal agents (5). However, none of them were formally confirmed as actually responsible for Crohn’s disease (CD), one of the two entities of IBD.

Most animal models, including 2,4,6-tri-nitrobenzenesulfonic acid (TNBS)-induced colitis in mice and rats, have been described as “mediated” by type 1 cytokines. Indeed, chronic intestinal lesions are associated with an increased synthesis of proinflammatory and type 1 cytokines (5, 6). However, more recent studies have demonstrated the importance of type 2 cytokines for the induction of colitis. In TCR-α−/− animals (TCR-α−/−) spontaneously de-
veloping colitis (7), acute lesions are associated with an increased IL-4 synthesis (8) and with local IgE production (9), whereas chronic lesions are associated with type 1 cytokines (8). Indeed TCR-α−/− × IL-4−/− mice do not develop colitis, whereas colitis in TCR-α−/− × IFN-γ−/− animals is similar to the pathology observed in TCR-α−/− × IFN-γ+ mice (10). Mucosal immune response is associated, in TCR-α−/− and IL-2−/− mice, to IgE synthesis (9, 11), and is dependent on luminal bacteria (12, 13). Additionally, in TNBS-induced colitis, disruption of the IL-4 gene or administration of anti-IL-4 antibodies attenuates the severity of the lesions, whereas disruption of the IFN-γ gene leads to an increased pathology (14). The respective roles of type 1 and type 2 cytokines have been further delineated using the same model. Indeed, a recently published study has shown that Th1-like cytokine responses were inducing fatal, acute, transmural, and focal types of lesions, whereas Th2-like cytokine responses were playing a significant role in the diffuse atrophic changes in crypts and the mucosal layer that occur in the late stages of this disease (15).

Recently, we have shown that divergent mucosal cytokine patterns evolved during the different stages of CD. A type 2 pattern with prominent IL-4 response and local production of IgE is associated with the early intestinal lesions of patients with CD and followed by a type 1 response in the chronic lesions of the same patients (16, 17). Furthermore, it has been shown that the enhancement of intestinal permeability observed in patients with CD is associated with an increase of activated B cells (CD45 RO+CD19+), which have the capacity to synthesize IgE (18). Additionally, we have demonstrated, in patients with type 2 and IgE-mediated disease like atopy or asthma, the presence of an airway-like inflammation of the gut, including high levels of type 2 cytokines (19) and an increase of the intestinal permeability (20). Taken together, these results suggest that the common mucosal immune system could modify the intestinal permeability and therefore bacterial translocation through mechanisms involving IL-4/IgE and/or FcεRI, the high affinity IgE receptor.

Evidences for a role of the endogenous bacterial flora in the bowel inflammation have also been accumulating (5). In humans, the importance of bacterial flora was demonstrated in a model of postsurgery relapse, which occurs at a rate of 73% after 1 yr (21). If the anastomosis is isolated from the fecal stream, no lesion occurs, whereas the relapse is rapid after the infusion of intestinal luminal content (22). We thus hypothesize that, in CD, lesions are due either to compounds from the digestive flora or to virulent bacteria invading the digestive tract in a patient with a defective immune intestinal response. Indeed flora from stool samples, obtained in patients with CD, contains higher concentrations of anaerobic bacteria, among others Bacteroides vulgatus and some coccobacilli (Eubacterium, Peptostreptococcus, and Coprococcus [23]). Likewise, a significant increase in the number of luminal ileal and colic Bacteroides fragilis and Escherichia coli was observed (24, 25), as well as an increase of mucosal enterobacteria in biopsies (26). However, it has not been so far formally demonstrated that such bacteria were the causal agent of the disease. It is rather suspected that the presence of these bacteria worsen the symptoms initiated by alterations of the immune system. In most animal models of spontaneous colitis, the severity of the inflammatory lesions increases with the presence of the bacterial flora (6, 12, 27).

Using hFcεRIα Tg and FcεRI-deficient animals, we investigated if IgE receptor expression was affecting inflammatory parameters, bacterial flora and its translocation towards mesenteric lymph nodes (MLNs) in naive animals. Our results suggest that FcεRI might be able to contribute to the development of intestinal inflammation, possibly due to increased levels of IL-4.

Materials and Methods

Animals. Human FcεRIα Tg and FcεRIα−/− mice that have been described elsewhere (2–4) are in a Balb/c background. Unless specified, animals aged between 8 and 16 wk as well as corresponding wild-type (WT) Balb/c were raised in a specific pathogen-free (SPF) facility, under a 12:12 h day–night illumination cycle. Tap water was available ad libitum and animals were fed with standard mice chow (D04; UAR).

Experimental Procedures. Animals were killed by cervical dislocation. MLNs were first aseptically removed before intestinal resection and placed immediately in cysteinated-strength Ringer’s medium for microbiological analyses. Then, transpapillary samples of distal colon and ileum were resected and fixed in 4% paraformaldehyde (PFA) or snap frozen in liquid nitrogen, respectively, for histologic examination and cytokine quantification. Samples of feces were put in the same medium as above for microbiological analyses.

Microbiological Analyses. MLNs and feces were weighted. Incubations were performed within 4 h after animal sacrifice. Cultures for both aerobic and anaerobic flora were performed on Columbia blood agar either by direct inoculation or after an enrichment in liquid Wilkins-West medium for detection of germs present in small amounts. Anaerobic conditions were obtained in hermetic jar using Anaerogen (Oxoid) reagent.

Results were expressed as log CFU per gram of feces for both total counts and counts of identified bacteria. Detection limit for mesenteric tissue was ~10 germ/g of tissue.

Reverse Transcription PCR. Frozen colon samples were placed in Trizol (Life Technologies), and total RNA was extracted according to the manufacturer’s instructions (Bioprobe). Quantitative reverse transcription (RT)-PCR was performed exactly as described previously (16). pQB3 and pMus-3 were respectively used as competitor for β-actin and for IL-1β, IL-6, TNF-α, IL-10, IFN-γ, and IL-4 (a gift from Dr. D. Shire, Sanofi Elf Bio Recherches, Labege, France). The size of the amplified fragments and the sense and antisense primers are figured on Table I. FcεRI and IgE mRNA levels were determined by semiquantitative RT-PCR. A fixed amount of cDNA, corresponding to the lowest number of β-actin cDNA molecules in the group of samples, was used. Results were expressed as absorbance units (at 260 nm) per molecule of β-actin mRNA.

IgE Measurements. Serum IgE concentrations were measured as described previously (28). In brief, 96-well microtiter plates (Maxisorb; Nunc) were coated overnight at 4°C with 2 μg/ml purified anti–mouse IgE (clone R35-72; BD PharMingen) in PBS buffer, pH 7.4. After washing, wells were saturated with PBS–1% BSA. After washing, samples or anti–TNP IgE (clone 26 IgE Receptor in Bacterial Translocation and Intestinal Inflammation
C48-2; BD PharMingen), used for the standard curve, were added and incubated overnight at 4°C. After washing, biotinylated anti-IgE antibody (2 μg/ml, clone R35-92; BD PharMingen) was incubated for 1 h at room temperature. After washing, plates were then incubated for 30 min at room temperature with streptavidin-conjugated horseradish peroxidase (1:10,000; Jackson ImmunoResearch Laboratories) and reactions were revealed by incubation to water for 3 h. Then, each mouse was given, by gavage, 8 ml 50% ethanol saline or saline alone. Animals were killed 48 h later. Macroscopic lesions were assessed according to the score established by Wallace et al. (32).

Pathological Analyses. 4-μm paraffin sections were stained with May–Grünwald/Giemsa and examined for morphology and presence of inflammatory infiltrates. Microscopic inflammatory score was measured according to Ameho et al. (29).

Intestinal Permeability. Intestinal permeability was measured according to Meddings and Gibbons (30). Mice were denied access to water for 3 h. Then, each mouse was given, by gavage, 8 mg mannitol, 12 mg lactulose, and 6 mg sucrose in 200 μl drinking water. Groups of five mice were placed into stainless steel metabolic cages in order to separate feces from urine. Animals in the feces, number of bacteria in the MLN, and cytokine cDNA levels in the Tg and WT mice were analyzed by the Kruskall-Wallis test. Differences were statistically significant if the P value was <0.05.

Results

To study the role of FcεRI on intestinal inflammation, three different strains of mice expressing FcεRI at different levels and with a different cell distribution were compared: WT Balb/c mice expressing FcεRI only on mast cells and basophils, hFcεRIα Tg mice expressing a functional humanized receptor on mast cells, basophils, monocytes, eosinophils, and epidermal Langerhans cells, and FcεRIα−/− animals in which receptor expression is absent. To correlate receptor expression levels with the observed phenotype, steady-state levels of FcεRIα mRNA were determined in colonic samples using semiquantitative RT-PCR. Primers were chosen in regions displaying 100% homology between human and mouse, so that amplification efficiency was identical in WT and hFcεRIα Tg mice. Fig. 1 (top) shows that receptor expression is ~8.5-fold higher in Tg than in WT animals. As expected, no mRNA amplification was detected for FcεRIα−/− animals.

Igs. To rule out that differences in IgE levels between the groups of animals would be superimposed to differential expression of the receptor, presence of the productive transcript for IgE was assessed in the colon by semiquantitative RT-PCR. No differences were observed in the samples from the three groups of mice (Fig. 1, bottom), showing that IgE production by intestinal plasmocytes was comparable. Likewise, total IgE concentrations in the se-
rum were also measured by ELISA. Human FcεRIα Tg, Balb/c, and FcεRIα−/− mice were presenting comparable levels of IgE (2.46 ± 1.64, 2.40 ± 0.99, and 1.80 ± 0.93 μg/ml, respectively).

**Human FcεRIα Tg and FcεRIα−/− Mice Do Not Develop Spontaneous Colitis and Display Normal Intestinal Morphology.** Macroscopic and microscopic aspects of the digestive tract from hFcεRIα Tg, FcεRIα−/−, and corresponding Balb/c mice housed in an SPF facility were then examined. No differences could be observed between the animals in the three groups in either colon or ileum. No sign of spontaneous colitis or inflammation was detectable in any of the animals examined (null score for both macroscopic and microscopic inflammation, absence of eosinophilia, and of mast cell degranulation; Fig. 2).

**Human FcεRIα Tg Mice Express Increased Levels of Colonic IL-4.** Alterations in cytokine patterns have been evidenced in spontaneously occurring as well as in experimentally induced colitis. To determine if levels of FcεRI expression would affect intestinal cytokine production, mRNA for proinflammatory (IL-1β, TNF-α) and immunoregulatory (IL-10, IFN-γ, and IL-4) cytokines were analyzed in colon and small intestine samples of hFcεRIα Tg, WT, and FcεRIα−/− mice, using quantitative RT-PCR. No differences in cytokine mRNA were observed in small intestine. However, in the colon from hFcεRIα Tg mice, IL-4 and IL-10 levels were respectively increased four- and fivefold compared with WT animals, whereas, in FcεRIα−/− animals, IFN-γ was increased fourfold when compared with WT (Fig. 3). Cytokine levels in the colon and IL-4 in particular were thus differing from one group to the other.

**Human FcεRIα Tg Mice Display Increased Intestinal Permeability.** IL-4 has been shown to affect transcellular and paracellular antigen transport across intestinal epithelium in vitro (33). Small intestine and colon permeability were thus measured in vivo, in the three groups of animals, by gavage with lactulose, mannitol and sucralose, followed by measurements of urinary sugar concentrations. Urinary lactulose/mannitol ratio (a marker of small intestinal permeability) was increased 5.4-fold in hFcεRIα Tg animals compared with both WT and FcεRIα−/− mice, and the colon permeability evaluated by lactulose/sucralose ratio was comparable (Fig. 4). This suggests that differences in the intestinal permeability between the mouse strains are mainly restricted to the small intestine and do not affect colon.

**Figure 1.** Expression of FcεRIα transcripts (top), β-actin (middle), and IgE productive transcripts (pe; bottom) in hFcεRIα Tg, WT, and FcεRIα−/− mice. Ethidium bromide–stained agarose gels were loaded with amplified PCR products from individual mice.

**Figure 2.** Histology of colon mucosa from hFcεRIα Tg, WT, and FcεRIα−/− mice after May-Grünwald/Giemsa staining of paraffin-embedded 4-μm sections. Bars, 0.2 mm.
To detect potential alterations in tight junctions, the main element controlling paracellular transport across the epithelium, immunohistochemistry was performed to detect occludin and ZO-1, two major proteins of the tight junction complex (34). Specific staining for occludin was detected on colon and small intestine preparations from the three groups of animals. No differences were observed between the groups. No ZO-1 staining was observed on any intestine sections, whereas Z0-1 mRNA was detected by RT-PCR on the same samples and kidneys of the same animals showed a strong positive immunostaining (data not shown). Taken together, these data suggest that elevated transcellular rather than paracellular permeability is accounting for the increased permeability in the small intestine from hFcRIα Tg mice.

Human FcRIα Tg Mice Have an Altered Bacterial Flora and Display Increased Translocation towards MLNs. As an increased intestinal permeability might facilitate the translocation of bacteria to the gut lumen and would thus give way to potential infection and inflammation, bacterial flora in the lumen and in MLNs from hFcRIα Tg, FcRIα−/−, and WT mice was compared (Fig. 5). Total numbers of aerobic and anaerobic germs were similar in the feces from the three groups of animals. Lactobacillus appeared as the most prominent genus. Interestingly, Bacteroides in hFcRIα Tg
animals were ~5,000- and 50-fold more abundant than in WT and FcεRIα−/− animals, respectively. Bifidobacterium was ~40-fold more abundant in FcεRIα−/− than in the two other groups (Fig. 5 a). No significant differences between the three groups were found for other germs. These data show that the status of FcεRI expression influences the relative composition of the fecal flora.

Compared with fecal flora, the number of germs present in the MLNs was lower by six to seven orders of magnitude in the three types of animals (Fig. 5 b). Overall, translocation was 50- and 30-fold higher in hFcεRIα Tg mice than in WT animals and FcεRIα−/−, respectively. Lactobacillus species were overwhelmingly dominant. Lactobacillus brevis, Lactobacillus lactis lactis, and Lactobacillus plantarum were the identified species present. Occasionally, E. coli or Enterococcus species were isolated. As expected for a strictly anaerobic strain, no Bacteroides were translocating to the MLNs. Thus, additional expression of FcεRI in hFcεRIα Tg mice promotes selective translocation of mainly non-pathological aero-anaerobic bacteria from the lumen to the MLNs, in the absence of intestinal inflammation.

As some colitis-prone strains, such as IL-2–deficient mice, do not develop pathology when housed in germ-free conditions (12), we investigated if mice maintained in a conventional facility, rather than in an SPF facility, would develop colitis or inflammation. Animals were killed 1 mo after their transfer from the SPF facility. No colitis or morphological alterations were detected in any of the three strains. Along the same lines, data obtained for the composition of the flora and its translocation towards MLNs were not statistically different from those observed for SPF-raised mice (not shown). Environmental conditions do not appear to greatly affect the bacterial flora in any of the three strains of mice.

**Discussion**

In this study, we investigated the effects of FcεRI expression on intestinal inflammation using hFcεRIα Tg mice, which express the high affinity receptor with a cell distribution similar to that found in humans, WT, and FcεRIα−/− mice. Indeed, in contrast to humans, mice are lacking high affinity IgE receptor expression on eosino-
phils, macrophages, and platelets, making them inadequate to fully evaluate IgE-dependent inflammation.

No sign of inflammation, eosinophilia, or mast cell degranulation were detected in any of the three strains of mice; however, increased levels of IL-4 were detected in the colon from hFcεRIα Tg animals. This cytokine has been shown to increase epithelial permeability in vitro (33). Furthermore, an increase in intestinal permeability was observed in patients with type 2–associated pathologies and IgE such as atopy and asthma (20). In vivo measurements of intestinal permeability revealed an increased lactulose/mannitol ratio but no changes in lactulose/sucralose ratio in hFcεRIα Tg mice. This indicates that, in these animals, small intestine permeability rather than colonic permeability was affected. Increased expression of IL-4 in hFcεRIαTg mice associated with an increased permeability of the small intestine is thus fully in agreement with these previous experimental and clinical observations.

A modification of the intestinal flora and an increased bacterial translocation in the absence of spontaneous colitis were observed only in hFcεRIα Tg mice. The three groups of mice were on the same Balb/c background and raised in the same room, therefore excluding any bias due to genetic factors in the results. Furthermore, no significant difference in the fecal flora was detected, whether animals were raised in a SPF or in a regular animal facility. This

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<th>hFcεRIα Tg</th>
<th>WT</th>
<th>FcεRIα−/−</th>
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<tr>
<td>Death rate</td>
<td>4/7</td>
<td>1/6</td>
<td>0/6</td>
</tr>
<tr>
<td>Macroscopical score</td>
<td>4.6 ± 2</td>
<td>1.6 ± 2.3</td>
<td>0.33 ± 0.8</td>
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<tr>
<td>Histological score</td>
<td>3.33 ± 2.5</td>
<td>1.4 ± 2.6</td>
<td>1.16 ± 1.19</td>
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Scores were determined according to Ameho et al. (reference 28) and Wallace et al. (reference 31). Results are expressed as mean ± SD.
suggests that the composition of the flora was not modified according to the external environment. Similarly, no quantitative differences in the fecal flora between the three groups of animals were detected. In contrast, major qualitative differences were observed. Indeed, Bacteroides was 5,000- and 50-fold more abundant in hFcεRIαTg than in WT and FcεRI-deficient animals, respectively. These strictly anaerobic bacteria have been associated in the colitis occurring in a rat model with a modified immune system (HLA-B27/β2 microglobulin Tg animals). Indeed, the normal endogenous flora (containing Bacteroides) is sufficient to trigger colitis in these animals, whereas non-Tg animals harboring the same flora do not develop colitis. Colitis in Tg rats can only be prevented by keeping the animals in germ-free conditions (35). Furthermore, increased number of B. vulgatus are found in feces from patients with CD (23). Likewise, a significant increase in the number of luminal ileal and colic B. fragilis has been observed (24). Finally, Bacteroides was also associated to an extra-intestinal inflammatory pathology. Indeed, a comparative study between healthy Estonian (country with low atopy prevalence) and Swedish (country with high atopy prevalence) 1-yr-old children, has shown that the former had higher number of Lactobacilli and Eubacteria, whereas the later displayed higher number of Bacteroides and Clostridia (36). Increased population of Bifidobacterium, which are 40-fold more abundant in FcεRI-deficient animals, have been involved in the development of gut-associated lymphoid tissue in neonates and in particular in the regulation of type 2 responses in mice (37). Levels of FcεRI expression and differences in receptor cellular distribution thus affect the composition of fecal flora.

As expected after the permeability measurements, bacterial translocation from the intestinal lumen towards MLNs was also affected by FcεRI expression. The increased spontaneous translocation observed in hFcεRIα Tg animals was mainly affecting Lactobacillus. There were no Bacteroides found in MLNs from any strain of animal. Indeed, it has been reported that aerobes such as Lactobacillus are very efficiently translocated, whereas anaerobic germs, such as Bacteroides, poorly translocate (38). Would some anaerobic bacteria cross the intestinal wall and reach the peritoneal cavity, they would not withstand the aerobic environment and thus do not survive lest proliferate.

Although mechanisms of bacterial translocation are still unclear, it is considered that bacteria are either crossing the intestinal wall by a transcellular way or taking a paracellular route (38). In this later case, a disruption or some loosening of the tight junctions maintaining the integrity of the epithelial barrier would have to take place. However, no modification of occludin expression was detected by immunohistochemistry. As tight junctions do not seem to be affected, it is likely that an increased transcellular passage of bacteria is responsible for the increased bacterial translocation. There is no report so far on Lactobacillus-specific transcytosis mechanisms. It has been reported that Campylobacter jejuni were translocating across Caco-2 cells using a paracellular way (39). Likewise, E. coli isolated from patients with necrotizing enterocolitis were transcytosed in vitro in the absence of ultrastructural changes (40).

In the present model of acute TNBS-induced colitis (31), strikingly different effects were observed on the three strains of mice. FcεRI-deficient mice were completely protected from colitis, suggesting that FcεRI expressed on mast cells (and basophils) was involved in the pathology onset. By contrast, colitis in hFcεRIαTg mice was exacerbated, even leading to a high death rate. Higher IL-4 levels in these colitis-sensitive animals are in agreement with the inhibition of chronic (10 d) TNBS-induced colitis in IL-4-deficient animals (14) and with the absence of colitis in TCR-α−/− × IL-4−/− animals (10). Furthermore, the increased number of Bacteroides found in hFcεRIα Tg might also have increased the severity of colitis, as demonstrated previously on TNBS-induced colitis in rat (41, 42). Finally, additional FcεRI expression on eosinophils and macrophages compared with WT animals might also contribute to the increased pathology by affecting the intestinal barrier.

hFcεRIαTg mice might thus be considered in a state of “pre-IBD” with increased number of luminal Bacteroides, increased Lactobacillus translocation to the MLNs, increased small intestinal permeability, higher colonic levels of IL-4, but no macroscopic or microscopic symptom of inflammation. Along these lines, increase of intestinal permeability (measured by lactulose/mannitol ratio) in the absence of a clinical sign of inflammation has been considered as a predictive marker of relapse in patients with remitting CD (43, 44).

If bacterial flora has been shown to influence the development of immune responses (45), we have reported here that alterations of the immune system were also able to affect bacterial flora and its translocation. Besides the involvement of FcεRI in susceptibility to intestinal inflammation, we have recently obtained evidences that IgE was also increasing susceptibility to colitis (Nutten, S., manuscript in preparation). Thus, pharmacological targeting of IgE or its high affinity receptor, with reagents such as nonanaphylactogenic anti-IgE antibodies, would therefore be potentially useful for treatment of IBD. In this context, colitis-prone hFcεRIα Tg mice represent a valuable model to assess the potency of compounds, which would prevent the development of clinically detectable inflammation.

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