Leptin receptor expression on T lymphocytes modulates chronic intestinal inflammation in mice

B Siegmund, J A Sennello, J Jones-Carson, F Gamboni-Robertson, H A Lehr, A Batra, I Fedke, M Zeitz, G Fantuzzi

Background: Leptin regulates appetite through the long isoform of its receptor in the hypothalamus. Although leptin regulates immune responses, it is still unknown whether a direct effect of leptin on lymphocytes is required.

Aims: To clarify whether expression of leptin receptors on T lymphocytes modulates intestinal inflammation in mice.

Methods: The model of colitis induced by transfer of CD4-CD45RB$^+$ (RB$^+$) cells into scid mice was used. Wild-type (WT) or leptin receptor deficient (db/db) RB$^+$ cells were transferred into scid mice and development of colitis evaluated.

Results: Leptin receptors were expressed on both RB$^+$ and RB$^-$ cells. Intestinal lymphocytes of mice with leptin expressed high leptin levels compared with healthy controls whereas the opposite was true for serum leptin levels. Transfer of RB$^+$ cells from db/db mice induced delayed disease compared with transfer of WT cells. A high rate of apoptosis in lamina propria lymphocytes and reduced cytokine production were observed early on in scid mice receiving db/db RB$^+$ cells. These effects were not due to the high levels of glucocorticoids present in db/db mice as administration of corticosterone to WT mice failed to reproduce this phenomenon. High expression of peroxisome proliferator activated receptor $\gamma$ was observed in the colon of recipients of db/db RB$^+$ compared with WT cells. Freshly isolated db/db RB$^+$ cells produced low levels of interferon $\gamma$. Despite delayed onset of colitis, as disease progressed differences between mice receiving WT or db/db cells were no longer apparent.

Conclusions: These results suggest that leptin affects the immune response, partly by acting on the long isoform of its receptor expressed on T lymphocytes.

Leptin is best known for its ability to regulate food intake and metabolism. Leptin regulates appetite through the long isoform of its receptor in the hypothalamus. Although leptin regulates immune responses, it is still unknown whether a direct effect of leptin on lymphocytes is required. To clarify whether expression of leptin receptors on T lymphocytes modulates intestinal inflammation in mice, the model of colitis induced by transfer of CD4-CD45RB$^+$ (RB$^+$) cells into scid mice was used. Wild-type (WT) or leptin receptor deficient (db/db) RB$^+$ cells were transferred into scid mice and development of colitis evaluated.

Results: Leptin receptors were expressed on both RB$^+$ and RB$^-$ cells. Intestinal lymphocytes of mice with leptin expressed high leptin levels compared with healthy controls whereas the opposite was true for serum leptin levels. Transfer of RB$^+$ cells from db/db mice induced delayed disease compared with transfer of WT cells. A high rate of apoptosis in lamina propria lymphocytes and reduced cytokine production were observed early on in scid mice receiving db/db RB$^+$ cells. These effects were not due to the high levels of glucocorticoids present in db/db mice as administration of corticosterone to WT mice failed to reproduce this phenomenon. High expression of peroxisome proliferator activated receptor $\gamma$ was observed in the colon of recipients of db/db RB$^+$ compared with WT cells. Freshly isolated db/db RB$^+$ cells produced low levels of interferon $\gamma$. Despite delayed onset of colitis, as disease progressed differences between mice receiving WT or db/db cells were no longer apparent.

Conclusions: These results suggest that leptin affects the immune response, partly by acting on the long isoform of its receptor expressed on T lymphocytes.

Abbreviations: db/db, leptin receptor deficient mice; WT, wild-type mice; PPAR$\gamma$, peroxisome proliferator activated receptor $\gamma$; LEPR, leptin receptor; IFN-$\gamma$, interferon $\gamma$; IL, interleukin; TGF-$\beta$, transforming growth factor $\beta$; Th1, T helper 1; IEL, intraepithelial lymphocytes; LPL, lamina propria lymphocytes; MLN, mesenteric lymph node cells; MIP-2, macrophage inflammatory protein 2; TNF-$\alpha$, tumour necrosis factor $\alpha$; GC, glucocorticoids; CS, corticosterone.
glucocorticoids. Therefore, the possible contribution of these factors is eliminated.

METHODS

Mice

Animal protocols were approved by the animal studies committee of the University of Colorado Health Sciences Center. Six to eight week old male C57BL/KS db/db mice (C57BLKS/J-+/+Lepr+/+H2b) and their non-obese (+/− and db+/−) littermates, as well as Balb/c mice, were obtained from the Jackson Laboratories (Bar Harbor, Maine, USA). Six to eight week old male Balb/c scid mice were from Charles River (Wilmington, Massachusetts, USA). Experiments were replicated using db/db mice and their non-obese littermates in a C57BL/6 background (Jackson Laboratories) (H2b). In this case, C57BL/6 scid mice were used as recipients (Jackson Laboratories). For experiments evaluating the role of glucocorticoids in the development of colitis, WT C57BLKS/J received drinking water supplemented with corticosterone phosphate (Sigma Chemicals, St Louis, Missouri, USA) at 2 mg/ml for one month prior to isolation of splenocytes. Serum corticosterone levels were measured using an ELISA kit from Assay Designs, Inc. (Ann Arbor, Michigan, USA).

Cell sorting, administration, and culture

A splenocyte suspension from WT and db/db mice was prepared. CD4+ cells were positively enriched using L3T4 magnetic microbeads (Miltenyi Biotec, Auburn, California, USA) and sorted into RBhigh and RBlow cells. Sorted RBhigh cells (4 × 10^6/mouse) were injected intraperitoneally into scid recipients. Alternatively, sorted RBhigh and RBlow cells were cultured for 48 hours at 2.5 × 10^3/ml in 96 well plates in the presence of plate bound anti-CD3ε antibodies (BD Pharmingen) at 1 μg/ml. Cells per sample. Staining with annexin V and propidium iodide (BD Pharmingen) was used for evaluation of the rate of apoptosis in LPL. Surface marker expression was evaluated using antibodies from BD Pharmingen and Caltag. Analysis was conducted on a FACSCalibur (BD Pharmingen) using the Cell Quest analysis program (BD Pharmingen). Markers evaluated included CD3, CD4, CD8a and CD8b (BD Pharmingen; 1 μg/ml) or murine recombinant leptin (R&D Systems, Minneapolis, Minnesota, USA; 1 μg/ml).

Clinical and histological assessment of colitis

Mice were weighed weekly and monitored for the appearance of diarrhoea and blood in the stools. A disease scoring system was applied, as previously described.13 Weights were ranked by assigning points as follows: 0 = 0–5% weight loss; 1 = 6–10% weight loss; 2 = 11–15% weight loss; 3 = 16–20% weight loss; and 4 = >20% weight loss. Appearance of diarrhoea was scored as follows: 0 = well formed pellets; 1 = pasty and semiformal stools that did not adhere to the anus; and 4 = liquid stools that did adhere to the anus. Appearance of blood in the stools was scored as follows: 0 = no blood using hemoccult (Beckman Coulter, Palo Alto, California, USA); 2 = positive hemoccult; and 4 = gross bleeding. Total scores given for wasting, diarrhoea, and stool blood were added and divided by 3 for a maximal disease score of 4. Post mortem, the entire colon was excised and a 1 cm segment of the transverse colon was fixed in 10% buffered formalin for histological analysis. Paraffin sections were stained with haematoxylin/eosin. Four to six colon rings were obtained from each 1 cm colon segment and were thus available for histological examination. Histological scoring was performed in a blinded fashion by a pathologist (HAL) as a combined score of inflammatory cell infiltration (0–3) and tissue damage (0–3), as described previously.16

Colon culture

A segment of the colon was removed, cut open longitudinally, and washed in phosphate buffered saline containing penicillin and streptomycin. The colon was then further cut into strips of approximately 1 cm² and placed in 24 flat bottom well culture plates containing 1 ml of RPMI supplemented with penicillin and streptomycin. Strips were incubated at 37°C for 24 hours. Culture supernatants were then harvested and assayed for cytokines.

Preparation of intraepithelial (IEL), lamina propria (LPL), and mesenteric lymph node (MLN) cells

IEL and LPL were isolated from the colon as described previously.7 Single cell suspensions of MLN were prepared by passing cells through a 100 μm strainer. LPL and MLN were cultured for 24 hours at 2.5 × 10^6/ml in 96 well plates in the presence of plate bound anti-CD3ε antibodies (BD Pharmingen) at 1 μg/ml.

Cytokine and leptin measurements

Murine IL-18, IL-10, macrophage inflammatory protein 2 (MIP-2), IL-10, and tumour necrosis factor α (TNF-α) levels were measured using an electrochemiluminescence method, as described previously.17 INF-γ, IL-4, IL-6, and leptin were measured using specific ELISA (BD Pharmingen and R&D Systems). TGF-β levels were measured after activation with HCl and subsequent neutralisation with an ELISA using anti-human TGF-β1 antibodies from BD Pharmingen.

Flow cytometry

Flow cytometry followed routine procedures using 1 × 10^5 cells per sample. Staining with annexin V and propidium iodide (BD Pharmingen) was used for evaluation of the rate of apoptosis in LPL. Surface marker expression was evaluated using antibodies from BD Pharmingen and Caltag. Analysis was conducted on a FACSCalibur (BD Pharmingen) using the Cell Quest analysis program (BD Pharmingen). Markers evaluated included CD3, CD4, CD8a and CD8b, CD25, CD69, and CD11b.

Immunohistochemistry

Frozen sections of transverse colon were analysed for expression of PPARγ using an antibody from Santa Cruz Biotechnology (California, USA) and a staining kit from R&D Systems.

Confocal microscopy

LPL and MLN were isolated from control mice and from scid mice that had received WT RBhigh cells eight weeks earlier. Cells were smeared on slides and fixed with 4% paraformaldehyde, air dried, and blocked with 10% normal goat serum. Cells were then incubated overnight with an antileptin

![Figure 1](https://example.com/image1.png)

Figure 1 Expression of leptin receptor (LEPR-B) on RBhigh and RBlow cells. Western blot analysis for LEPR-B was performed on sorted wild-type (WT) and leptin receptor deficient (db/db) RBhigh and RBlow cells (top panel). The bottom panel indicates equal protein loading, as evaluated by blotting with an antiactin antibody.
antibody (R&D Systems) or non-immune rabbit IgG as a negative control. After an overnight incubation, slides were washed and incubated with a secondary antibody conjugated to phycoerythrin. Nuclei were stained blue with bisbenzimide whereas sialoproteins were stained green using Alexa488 conjugated germagglutinin (Molecular Probes, Eugene, Oregon, USA). Slides were washed, mounted, examined using a Leica DM RXA confocal laser scanning system, and analysed with SlideBook Software.

Western blot
For evaluation of LEPR-B expression on RB\textsuperscript{high} and RB\textsuperscript{low} cells, sorted cells were resuspended in RIPA buffer and western blot analysis was performed as described previously\textsuperscript{14} using an antimurine LEP-R antibody (R&D Systems). For evaluation of T-bet levels, the same procedure was employed using an anti-T-bet antibody (Santa Cruz Biotechnology). A goat antiactin antibody (Santa Cruz) was used to control for protein loading.

Statistical analysis
Data are expressed as mean (SEM). Statistical significance of differences between treatment and control groups were determined by factorial ANOVA and a Bonferroni-Dunn procedure as a post hoc test. Statistical analyses were performed using Stat-View 4.51 software (Abacus Concepts, Calabasas, California, USA).

RESULTS
Expression of LEPR-B and effects of leptin on RB\textsuperscript{high} and RB\textsuperscript{low} cells
Unstimulated freshly sorted (>95% pure) RB\textsuperscript{high} and RB\textsuperscript{low} cells obtained from +/+ (WT) and \textit{db/db} mice were analysed by western blot for the presence of LEPR-B. Results indicated that in WT cells, LEPR-B was expressed to a comparable extent on both RB\textsuperscript{high} and RB\textsuperscript{low} cells. On the other hand, as expected, LEPR-B was not expressed in \textit{db/db} cells (fig 1). These results were confirmed by reverse transcription-polymerase chain reaction analysis of total RNA (not shown). Leptin was able to modulate cytokine production in RB\textsuperscript{high} but not in RB\textsuperscript{low} cells stimulated in vitro with anti-CD3/CD28. Although the in vitro effects of leptin on IFN-\(\gamma\) levels were inconsistent, a significant reduction of IL-6 and IL-10 production was observed in RB\textsuperscript{high} but not in RB\textsuperscript{low} cells cultured in the presence of leptin (table 1).

Expression of leptin in LPL and MLN of mice with colitis
To verify that leptin is expressed locally in intestinal inflammation, LPL and MLN were extracted from controls and from \textit{scid} mice transferred eight weeks earlier with WT RB\textsuperscript{high} cells. As shown in fig 2, cells extracted from diseased mice expressed high levels of leptin compared with cells obtained from healthy controls. However, at the same time, systemic leptin levels were significantly decreased in mice with colitis compared with healthy controls (3.46 (0.76) v 1.76 (0.53) in control v \textit{scid} transfer mice, respectively; \(n=5\), \(p<0.05\), probably due to the reduction in body weight that accompanies development of disease in this model.

\textit{db/db} RB\textsuperscript{high} cells induce delayed colitis compared with WT cells
Enrichment and sorting of CD4\textsuperscript{+} cells from the spleen of +/+, \textit{db/+}, and \textit{db/db} mice generated equivalent percentages of RB\textsuperscript{high} and RB\textsuperscript{low} cells from the different mouse strains, although the absolute number was reduced in \textit{db/db} mice, presumably due to their lymphoid atrophy.\textsuperscript{2} Cell viability did not differ between +/+, \textit{db/+}, and \textit{db/db} RB\textsuperscript{high} cells. No significant differences were observed between mice injected with +/+ or \textit{db/+} LEPR-B RB\textsuperscript{high} cells. Therefore, data obtained from mice injected with cells obtained from +/+ or \textit{db/+} mice were pooled and are presented together in each of the following figures as the WT group.
Evaluation of disease activity scores indicated significantly milder early disease in scid mice injected with db/db R^{high} cells compared with mice receiving WT cells (fig 3A). Differences between the two groups were significant up to week 8 post-injection and disappeared thereafter.

Disease scores were assessed at weeks 5, 8, and 12. (A) Disease activity scores. (B) Histological scores. (C) Histology at week 5 and week 12. Representative sections are shown from recipients of WT and db/db cells. Data are mean (SEM) of 20 mice per group. *p<0.05, **p<0.01, ***p<0.001 versus WT.

Evaluation of disease activity scores indicated significantly milder early disease in scid mice injected with db/db R^{high} cells compared with mice receiving WT cells (fig 3A). Differences between the two groups were significant up to week 8 post-injection and disappeared thereafter.

Histological examination of the colon at five weeks revealed marked inflammation in mice injected with WT cells whereas we observed almost no inflammation in mice receiving db/db cells (fig 3B, 3C). However, this difference was no longer present when colon sections were examined at eight and 12 weeks post-transfer (fig 3B, 3C).

Results presented above were obtained using mice in a C57BLKS/J background. However, comparable data were generated when mice in a C57BL/6 background were utilised (not shown).
observed in mice treated with db/db RB<sup>high</sup> cells—we did not find significant differences in terms of differentiation into CD<sup>8+</sup> cells or expression of homing receptors between mice injected with WT and db/db cells (data not shown). Furthermore, cell activation was evaluated by comparing surface expression of CD25 and CD69 on CD3<sup>+</sup> MLN in scid mice injected with either WT or db/db cells and no significant differences between the two groups were observed (data not shown).

Interestingly, at five weeks post-treatment, mice injected with db/db cells had a rate of apoptosis in the LPL population similar to that of untreated Balb/c mice whereas apoptosis was markedly reduced in LPL of mice injected with WT cells (fig 4). However, the difference in LPL apoptosis between recipients of WT and db/db cells was no longer evident at 12 weeks post-injection. At this time point, apoptosis of WT LPL was no longer reduced compared with LPL obtained from control mice or mice receiving db/db cells (fig 4).

**Reduced early cytokine production in mice receiving db/db RB<sup>high</sup> cells**

Cytokine production was measured in colon cultures and in LPL cultures of mice receiving WT or db/db cells. Production of the cytokines and chemokines IFN-γ, IL-6, IL-18, and MIP-2 was significantly reduced in cultures obtained from the colon of recipients of db/db cells compared with recipients of WT cells at five weeks post-injection (fig 5). However, when these cytokines were measured 12 weeks post-injection, differences between recipients of WT or db/db cells were no longer present. The opposite results were obtained for IL-4, whose levels were similar early in disease but significantly lower in recipients of db/db cells at 12 weeks post-injection. No significant differences between recipients of WT and db/db cells were observed in terms of TGF-β production. TNF-α and IL-10 were below detection limit in each of the colon cultures evaluated. Similar results were obtained with cultures of anti-CD3-stimulated LPL (fig 6).

**Increased expression of PPARγ in the colon of mice receiving db/db RB<sup>high</sup> cells**

The nuclear receptor PPARγ has anti-inflammatory activities. We compared expression of PPARγ in the colon of mice that were transferred with WT or db/db RB<sup>high</sup> cells five or 12 weeks earlier. As shown in fig 7, expression of PPARγ was higher in the colon of mice that had received db/db compared with WT RB<sup>high</sup> cells, irrespective of the time point analysed.

**Reduced cytokine production in freshly sorted db/db RB<sup>high</sup> cells**

We evaluated production of IFN-γ and IL-10 in freshly sorted WT and db/db RB<sup>high</sup> and RB<sup>low</sup> cells. As expected, when stimulated with anti-CD3, alone or in combination with anti-CD28, WT RB<sup>high</sup> cells produced high levels of IFN-γ (fig 8A, B). Interestingly, db/db RB<sup>high</sup> cells stimulated with anti-CD3 alone produced low levels of IFN-γ which were not different from those produced by RB<sup>low</sup> cells (fig 8A). Costimulation with anti-CD3 and anti-CD28 overcame the reduced ability of db/db RB<sup>high</sup> to produce IFN-γ (fig 8B). In contrast, as expected, IL-10 was mostly produced by RB<sup>low</sup> cells and no significant differences between WT and db/db cells for production of this cytokine could be observed (fig 8C, D).

The transcription factor T-bet regulates production of IFN-γ. We investigated whether the reduced ability of db/db RB<sup>high</sup> to produce IFN-γ could be secondary to low levels of T-bet and therefore due to failure to differentiate...
DISCUSSION

The results of the present studies indicate that a selective deficiency of LEPR-B on T lymphocytes leads to delayed development of intestinal inflammation. These results are in agreement with our previous observations indicating protection from colitis in ob/ob mice. However, those previous data left open the question of whether a central or peripheral mechanism was involved in the observed effect.

The possible participation of a local leptin network in regulating intestinal inflammation is underscored by the presence of leptin receptors on both RB high and RB low cells and by expression of high leptin levels in LPL and MLN obtained from mice with intestinal inflammation. Furthermore, leptin modulated cytokine production in RB high cells. On the other hand, the observation that intestinal inflammation was associated with reduced systemic leptin levels suggests that it is local rather systemic leptin that participates in the modulation of inflammatory responses.

Administration of db/db RB high cells to scid mice induced significantly delayed disease compared with injection of WT cells. Recipients of db/db cells were not completely protected from colitis but did eventually develop disease. This indicates...
that the absence of LEPR-B does not completely alter the biological activity of RB\textsuperscript{high} cells. The current understanding of the disease inducing ability of RB\textsuperscript{high} cells proposes that, in the absence of regulatory T cells and suppressive cytokines in T cell deficient recipients, the aggressive T1 skewed donor RB\textsuperscript{high} cells undergo uncontrolled proliferation and activation, leading to colitis development.\textsuperscript{23} The observation that RB\textsuperscript{high} cells is necessary for the cells to fully express their direct effect of leptin on LEPR-B expressed on transferred cells.\textsuperscript{971} Two possible interpretations exist for the present results: (i) a high rates of apoptosis while LPL from Crohn’s disease patients are resistant to apoptotic stimuli.\textsuperscript{25} Previous results indicated that leptin acts as a protective factor in T lymphocyte apoptosis.\textsuperscript{10,26} In particular, in previous studies we observed high rates of apoptosis in LPL of \textit{db/db} mice which correlated with resistance in models of intestinal inflammation.\textsuperscript{7} In the present report, we showed that, compared with non-diseased animals, apoptosis was reduced early in disease in the LPL of \textit{scid} mice that received WT RB\textsuperscript{high} cells and that has been implicated in the regulation of inflammatory responses.\textsuperscript{21,24} is higher in recipients of \textit{db/db} compared with WT cells, indicating that indirect mechanisms might contribute to the observed effects.

Lamina propria lymphocytes from normal subjects exhibit high rates of apoptosis while LPL from Crohn’s disease patients are resistant to apoptotic stimuli.\textsuperscript{25} Previous results indicated that leptin acts as a protective factor in T lymphocyte apoptosis.\textsuperscript{10,26} In particular, in previous studies we observed high rates of apoptosis in LPL of \textit{ob/ob} mice which correlated with resistance in models of intestinal inflammation.\textsuperscript{7} In the present report, we showed that, compared with non-diseased animals, apoptosis was reduced early in disease in the LPL of \textit{ob/ob} mice which correlated with resistance in models of intestinal inflammation.21,24 is higher in recipients of \textit{db/db} compared with WT cells, indicating that indirect mechanisms might contribute to the observed effects.

Production of proinflammatory cytokines such as IFN-γ, IL-6, IL-18, and MIP-2 was reduced early in disease in recipients of \textit{db/db} RB\textsuperscript{high} cells compared with mice injected

Figure 8  Cytokine production and T-bet expression in freshly sorted wild-type (WT) and leptin receptor deficient (\textit{db/db}) RB\textsuperscript{high} and RB\textsuperscript{low} cells. RB\textsuperscript{high} and RB\textsuperscript{low} cells were isolated from the spleen of WT and \textit{db/db} mice. Cells were stimulated with plate bound anti-CD3\textsubscript{e} in the absence (A, C) or presence (B, D) of soluble anti-CD28. Interferon γ (IFN-γ) (A, B) and interleukin 10 (IL-10) (C, D) levels were measured in culture supernatants. Data are mean (SEM) of four wells. ***p<0.001 versus WT RB\textsuperscript{high} cells. [E] Expression of T-bet was evaluated by western blot in unstimulated WT and \textit{db/db} RB\textsuperscript{high} cells. Equal loading was evaluated using an anti-actin antibody.

A induced enteritis.\textsuperscript{9} However, other possible candidates exist. For example, we have demonstrated that expression of PPARγ, a molecule whose levels are altered in \textit{ob/ob} and \textit{db/db} mice and that has been implicated in the regulation of inflammatory responses,\textsuperscript{21,24} is higher in recipients of \textit{db/db} compared with WT cells, indicating that indirect mechanisms might contribute to the observed effects.

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Production of proinflammatory cytokines such as IFN-γ, IL-6, IL-18, and MIP-2 was reduced early in disease in recipients of \textit{db/db} RB\textsuperscript{high} cells compared with mice injected
with WT cells. However, these differences were not evident when levels of anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β were evaluated. This indicates that reduced early inflammation in recipient of db/db RB\textsuperscript{high} cells cannot be attributable to complete failure to produce cytokines but rather to a selective reduction of proinflammatory mediators. Furthermore, early protection from disease is not due to production of high levels of anti-inflammatory mediators.

Th1 cytokines and transcription factors controlling Th1 development are critical mediators in the model of colitis induced by transfer of RB\textsuperscript{high} cells.\textsuperscript{2} Although the mechanism is currently unknown, leptin controls production of Th1 cytokines, mainly IFN-γ.\textsuperscript{3} In the present study, we observed that freshly isolated db/db RB\textsuperscript{high} cells produced significantly lower amounts of IFN-γ compared with WT cells when stimulated with anti-CD3, providing a potential mechanism explaining the lower aggressivity of db/db RB\textsuperscript{high} cells. However, costimulation with anti-CD3 and anti-CD28 led to comparable production of IFN-γ by WT and db/db RB\textsuperscript{high} cells, suggesting that defects in the costimulatory pathways might be involved.

A role for the Th1 inducing transcription factor T-bet in different models of colitis has been described.\textsuperscript{2,7} T-bet deficient cells produce low levels of IFN-γ and are unable to induce colitis in immunodeficient recipients, a pattern similar to the one we observed with db/db cells. However, we found that db/db RB\textsuperscript{high} cells express T-bet to the same extent as WT cells, thus excluding this putative mechanism.

In conclusion, our present work indicates that, in a model of chronic Th1 mediated intestinal inflammation, the signal transducing isoform of the leptin receptor is an important regulator of T cell activity.

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Authors’ affiliations

B. Siegmund, A. Batra, I. Fedke, M. Zeitz, Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Medizinische Klinik I, Hindenburgdamm 30, 12200 Berlin, Germany

J. A. Sennello, G. Fantuzzi, Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, USA

J. Jones-Carson, Department of Microbiology, University of Colorado Health Sciences Center, Denver, CO, USA

F. Gamboni-Robertson, Department of Surgery, University of Colorado Health Sciences Center, Denver, CO, USA

H. A. Lehr, Institute of Pathology, University of Mainz, Mainz, 55131, Germany

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