Interleukin 17 (IL-17) is an inflammatory cytokine that plays a protective role against intracellular parasites. The role of IL-17 during Leishmania infection remains controversial and poorly defined. We evaluated whether IL-17 participates in the host immune response to Leishmania infantum. IL-17A is present in sera from patients with visceral leishmaniasis and decreases after successful treatment. In C57BL/6 infected mice, higher production of IL-17A coincided with the peak of parasitism. Il17ra−/− mice were more susceptible to infection and also exhibited reduced inflammatory infiltration and interferon γ (IFN-γ)–expressing CD4+ T-cell frequencies than wild-type mice. The frequencies of FoxP3+CD4+ T cells and interleukin 10 (IL-10)–expressing CD4+ T cells were increased in Il17ra−/− mice. We also demonstrated that IL-17A acts synergistically with IFN-γ to potentiate NO production and leishmanicidal activity in infected macrophages. Therefore, our results indicate that L. infantum induces IL-17A production, which promotes the control of parasite replication by strengthening T-helper type 1 responses and NO production and prevents regulatory T-cell and IL-10–expressing T-cell expansion.

Keywords. Leishmania infantum; visceral leishmaniasis; IL-17; nitric oxide.

Leishmaniasis comprises a wide spectrum of diseases caused by intracellular Leishmania parasites. Among these diseases, visceral leishmaniasis, which is caused by both Leishmania donovani and Leishmania infantum [1], is the most severe manifestation and remains an important cause of human mortality and morbidity around the world. Visceral leishmaniasis is endemic in 65 countries, and 350 million people are estimated to be at risk of becoming infected [2].

In murine models of visceral leishmaniasis, interleukin 12 (IL-12) plays a central role by initiating a T-helper type 1 (Th1) cell response [3]. The Th1 profile is classically associated with protection against Leishmania parasites because of interferon γ (INF-γ) and tumor necrosis factor α (TNF-α) production [4, 5], and these cytokines trigger the synthesis of microbicidal molecules by infected macrophages [6]. In contrast, Th2 responses and antiinflammatory cytokines, such as interleukin 4, interleukin 5, and interleukin 13, contribute to susceptibility and disease progression [7, 8]. Interleukin 10 (IL-10) is another important regulatory cytokine that inhibits phagocytosis, as well as major histocompatibility complex class II and costimulatory molecule expression. IL-10 also affects the ability of macrophages to kill intracellular parasites, contributing to Leishmania growth and spread [9, 10].

IL-17 potentiates inflammatory and autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis [11, 12]. Further, IL-17–producing cells regulate the progression of tumors [13] and protect against Candida albicans infections [14]. The proinflammatory
effects of IL-17 occur as a result of the activation of inducible nitric oxide synthase (iNOS) and the induction of granulocyte macrophage colony-stimulating factor, interleukin 1, interleukin 6, interleukin 8, TNF-α, and several chemokines, potentiating the inflammatory reaction [15]. The induction of these inflammatory mediators suggests that IL-17 plays a role in intracellular parasite infections, as has been demonstrated during Trypanosoma cruzi infection [16]. However, the role of IL-17–producing cells in leishmaniasis remains controversial. In a model of cutaneous leishmaniasis caused by Leishmania major, IL-17 production is associated with disease progression because the lesion sizes in infected IL-17–deficient BALB/c mice were smaller than in control mice [17]; however, in human L. braziliensis infections, the opposite holds true [18]. Further, larger amounts of IL-17 were found in the serum of asymptomatic individuals with a delayed-type hypersensitivity reaction to L. donovani than in the serum of symptomatic patients [19], demonstrating that, along with Th1 cells, IL-17 plays a complementary role in human protection against visceral leishmaniasis. The mechanisms by which IL-17 mediates protection are not understood, and the role of IL-17 in L. infantum infection is completely unknown. Here, we demonstrated that IL-17 protects against infection and is associated with the downregulation of regulatory T cells and IL-10 production, while benefitting the Th1 response and improving the leishmanicidal activity of macrophages in an NO-dependent manner.

MATERIAL AND METHODS

Patients
Nineteen patients (12 males and 7 females; 2–44 years old) who visited the University Hospital of the Federal University of Sergipe with confirmed visceral leishmaniasis were enrolled in the study (Supplementary Table 1). Pregnant women and patients receiving immunosuppressive treatments or with comorbidities were excluded. The diagnostic criteria used for inclusion were the identification of Leishmania in bone marrow aspirates and the rK39 serological test (Kalazar Detect Rapid Test, InBios International, Seattle, WA). All patients were examined, and the following information was recorded: identification, clinical complaints, physical examination findings, and laboratory test results. Serum was collected prior to Glucantime treatment (day 0), after treatment (45–60 days), and 1 year after therapy (180–360 days). All patients had the symptoms cured after the treatment. Thirteen endemic controls, who were living in the same area as the patients but exhibited no signs of clinical disease, and 8 nonendemic controls, who were US citizens without exposure to the infection, were also recruited. All procedures involving humans were approved by the Ethics Committee of the University Hospital of the Federal University of Sergipe.

Mice, Parasites, and Infection
Eight-week-old male C57BL/6 (wild type [WT]), C57BL/6 Il17ra−/−, and C57BL/6 Il10−/− mice were housed in temperature-controlled rooms (22°C–25°C) at the animal facility of the Medical School of Ribeirão Preto-USP and received water and food ad libitum. All procedures were approved by the Ethics Committee in Animal Research of the FMRP-USP. Isolate HU-UFS14 of L. infantum was cultured in Schneider medium supplemented with 20% heat-inactivated fetal bovine serum, 5% penicillin and streptomycin (all from Sigma-Aldrich, St. Louis, MO), and 2% human male urine. The mice were intravenously infected with 105 L. infantum parasites in the stationary growth phase, and hepatic and splenic parasite burdens were determined using a quantitative limiting dilution assay [20, 21].

Real-Time Polymerase Chain Reaction (PCR)
Total RNA was extracted from tissues using the TRIzol reagent (Invitrogen, Carlsbad, CA) and the SV Total RNA Isolation System Kit (Promega, Madison, WI) according to the manufacturer’s instructions. Complementary DNA was synthesized using Transcriptase Reverse SuperScript III (Invitrogen). SYBR Green Mix–based real-time quantitative PCR assays were performed using the StepOnePlus Real-Time PCR System (Applied Biosystems, Singapore, Singapore, Malaysia). The mean threshold cycle (Ct) values of triplicate measurements were used to calculate the expression of the target gene, which was normalized to the housekeeping gene Hprt, using the 2−ΔΔCt formula.

Leukocyte Isolation and Flow Cytometry
Liver leukocytes were recovered using Ficoll-Paque PLUS gradient centrifugation. After processing, viability was assessed via Trypan blue exclusion, and the cell concentration was determined. For cytokine staining, the cells were preincubated with 20 ng/mL of PMA, 500 ng/mL of ionomycin, and Golgi Plug for 6 hours; permeabilized using a Cytotix/Cytoperm kit according to the manufacturer’s instructions; and stained with fluorochrome-conjugated anti–IL-17A, anti–IFN-γ, and anti–IL-10. For FoxP3 labeling, the Foxp3 Staining Kit was used according to the manufacturer’s recommendations. For each sample, a minimum of 200 000 cells were acquired using a FACSCanto II flow cytometer and analyzed using FlowJo software (Tree Star, OR, USA). All antibodies and kits used in this study were purchased from BD Biosciences (San Jose, CA).

Cell Culture, Tissue Homogenates, and Soluble Mediator Assays
Splenocytes were cultured at a density of 5 × 106 cells/mL in 48-well plates at a final volume of 0.5 mL and stimulated with 50 µg/mL of L. infantum crude antigen for 72 hours. To measure cytokine concentrations in the liver, tissue samples were harvested, weighed, and triturated in 0.5 mL of phosphate-buffered saline (PBS) containing protease inhibitor cocktail Complete (Roche Diagnostics, Mannheim, Germany). The
production of IL-17A in culture supernatants or in tissue homogenates was measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN), according to the manufacturer’s instructions. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using a kit from Labtest SA (Lagoa Santa, Brazil), according to the manufacturer’s instructions.

Histopathological Immunohistochemical Analyses

The mice were euthanized 0, 4 and 6 weeks after infection, and their livers were removed. The tissues were fixed in formalin, dehydrated in graded ethanol, and embedded in paraffin. Serial sections (5 µm) were cut and mounted on glass slides precoated with 0.1% poly-L-lysine (Sigma-Aldrich). Histological assessment was performed after routine hematoxylin-eosin staining. The area of the liver lesion was determined using Leica Qwin software (Mannheim, Germany).

For immunohistochemical reactions, the paraffin was removed from the tissues, and antigenic recovery was performed by heating in citrate buffer (pH 6.0), for 30 minutes at 37°C. Endogenous peroxidase was blocked using 3% H2O2, cells were permeabilized with Triton 0.5%, and nonspecific reactions were blocked with 1% bovine serum albumin (BSA). The sections were incubated overnight with a monoclonal rat anti-7/4 antibody (Abcam, Cambridge, MA), followed by incubation with a biotinylated secondary antibody and avidin-biotin complex (Vector Laboratories, Ontario, Canada). The reaction was detected with diaminobenzidine, and the sections were counterstained with hematoxylin.

Immunofluorescence

Cryopreserved liver tissues from WT and Il17ra−/− mice were fixed in cold acetone and washed in PBS. The slides were incubated in 0.5% Triton-X-100 in PBS for 15 minutes, and nonspecific sites were blocked with 1% BSA. The slides were incubated with a primary anti-iNOS antibody overnight. The sections were washed, a FITC-conjugated secondary antibody diluted in 0.01 M Hepes (pH 7.5) was added, and the nucleus was stained with DAPI (300 nM). The slides were mounted with Prolong and analyzed using the Leica QWin Quantitative Imaging software (Leica Microsystems). The results are expressed as the fluorescence intensity.

Macrophage Generation and Infection

Bone marrow cells were isolated from the femurs of naive 6–8-week-old WT and Il17ra−/− mice, and bone marrow–derived macrophage (BMDM) differentiation was performed as described previously [22]. BMDMs were incubated overnight with 10 or 100 ng/mL of recombinant IFN-γ (rIFN-γ; Invitrogen) and/or 30, 100, or 300 ng/mL of recombinant IL-17A (rIL-17A; Biosource-Life Technologies, CA, USA). The cells were subsequently infected with L. infantum at a multiplicity of infection of 5 or left uninfected. After 4, 48, and 96 hours of infection, the cells were collected and stained with Rapid Panotico (New Prov, Pinhais, Brazil) for analysis. NO2− production in the supernatants was assessed using the Griess assay.

Statistical Analysis

Statistical significance was analyzed using PRISM5 (GraphPad Software, La Jolla, CA). Data are expressed as the mean values (± SD). Differences were tested using an unpaired Student t test or the Mann–Whitney test for samples with nonparametric distributions.

RESULTS

L. infantum Infection Induces IL-17A Production

We first evaluated the levels of IL-17A in the sera from 19 patients with visceral leishmaniasis before and at different time points after treatment with Glucantime. Serum samples from uninfected subjects from endemic and nonendemic areas (normal subjects) were used as controls. Higher levels of IL-17A were measured in the serum from patients with visceral leishmaniasis before treatment (day 0) than in normal or endemic controls (Figure 1). We also observed that, during treatment, the levels of IL-17A decreased but remained significantly higher than those of normal subjects (Figure 1). To understand the role of IL-17 during the infection, we used an experimental model of visceral leishmaniasis in which C57BL/6 mice. High levels of il-17a messenger RNA (mRNA) expression were detected during weeks 4, 6, and 8 after infection in the spleens and livers of
infected mice (Figure 2A). Moreover, higher levels of IL-17A were measured in spleen and liver homogenates and in antigen-stimulated splenocyte culture supernatants from infected mice than in homogenates and splenocyte culture supernatants from controls (Figures 2B and 2C). These findings demonstrate that L. infantum infection in mice also results in IL-17A production.

**IL-17 Plays a Critical Role in Overall Infection Control**

To characterize the role of IL-17 in the control of parasite growth, Il17ra−/− mice and control littermates were infected with L. infantum, and parasite loads in their spleens and livers were quantified. Il17ra−/− mice harbored significantly more parasites in both target organs during weeks 1, 4, 6, and 8 after infection than WT animals (Figure 3A and 3B). Myd88−/− and iNOS−/− mice were used as positive controls. Surprisingly, Il17ra−/− mice exhibited reduced weights of both spleens and livers as compared to WT mice (Figure 3C and Supplementary Figure 1). These findings suggest that IL-17 plays a role in the control of parasite growth and may also contribute to the hepatosplenomegaly that is observed during visceral leishmaniasis. Histological analyses revealed that WT mice exhibited large areas of inflammatory tissue, starting during week 2 after infection (data not pictured) and peaking during weeks 4 and 6 after infection. Interestingly, a diffuse cell infiltration with a predominance of mononuclear cells was observed concentrating around portal tracts in WT mice during week 6 after infection (Figure 4A). In the absence of IL-17RA, the inflammatory infiltrate was reduced, and we observed smaller and more-compact granulomas (Figure 4A). While the inflammatory areas in the WT group were larger than 14 000 µm², with areas up to 300 000 µm² during weeks 4 and 6 after infection, sizes of inflammatory areas were 5000 µm² and 40 000 µm² in Il17ra−/− mice, respectively (Figure 4B). Figure 4B shows that the lesions areas were significantly lower in Il17ra−/− mice. Consistent with the size of the inflammation area, the total leukocyte counts during week 6...
after infection were significantly reduced in Il17ra−/− mice as compared to WT mice (Figure 4C). Nevertheless, lower levels of ALT and AST were detected in Il17ra−/− mice, indicating that less liver damage occurred in these animals (Figure 4D). Immunohistochemical analyses demonstrated that fewer neutrophils infiltrated the livers of Il17ra−/− mice than to the livers of WT mice (Supplementary Figure. 2). The reduction of the number of inflammatory cells in the absence of IL-17RA was concomitant with downregulated mRNA expression of Cxcl10 and Ccl5, as well as their respective receptors, Cxcr3 and Ccr5. Conversely, overexpression of mRNA for the typical Th2/regulatory T cell (Treg) chemoattractant mediators Ccl17 and Ccr4 [23] was observed in Il17ra−/− mice (Figure 4E). Altogether, the results demonstrated that IL-17 participates in parasite control but also potentiates an inflammatory reaction.

**IL-17 and IL-10 Undergo Reciprocal Regulation**

Because the absence of IL-17RA promoted an upregulation of Th2/Treg chemoattractants, which attract 2 populations that commonly produce IL-10, we next evaluated the production
of IL-10 during visceral leishmaniasis in the absence of IL-17RA. A significant 100.2% increase in the number of IL-10-producing CD3⁺CD4⁺ T cells in the spleen and a 147.34% increase in the number of IL-10-producing CD3⁺CD4⁺ T cells in the liver were observed in Il17ra⁻/⁻ mice as compared to WT mice during week 6 after infection (Figure 5A). A significant increase in the number of CD3⁺CD4⁺ IL-10–producing cells was also observed in Il17ra⁻/⁻ mice as compared to WT
mice (Figure 5B). In addition, levels of Foxp3 transcripts were significantly increased, and Gata3 expression was downregulated by 27.6% in the spleen and by 53.5% in the liver in Il17ra−/− mice (Figure 5D), suggesting that the IL-17A produced during infection modulates the IL-10 released by Treg cells and non-lymphocytes. To determine whether IL-10 also controls IL-17A production during L. infantum infection, we infected Il10−/− mice and analyzed both IL-17A and IFN-γ production. We observed a significant increase in the frequency of IL-17A– and IFN-γ–producing CD3+CD4+ T cells in the absence of IL-10 (Figure 5E). In addition, larger amounts of IL-17A were detected in the supernatants of spleen cell cultures from WT mice during ex vivo specific stimulation, compared with unstimulated cells. Interestingly, the ablation of IL-10 potentiated the

![Figure 5](image-url)

**Figure 5.** Il17ra−/− infected mice exhibit increased regulatory T-cell frequency and interleukin 10 (IL-10) production. A, Wild-type (WT) and Il17ra−/− mice were infected with 10⁷ Leishmania infantum in the stationary growth phase. The cells from the spleen and liver were harvested at week 6 after infection and stimulated with 20 ng/mL of PMA plus 500 ng/mL of ionomycin and Golgi Stop for 6 hours. The cells were gated on lymphocytes based on forward scatter and side scatter, and IL-10–expressing CD4+ T cells were analyzed in the CD3+ gate; the bars display the representative results from dot plots. B, Cells were stimulated as described for panel A, and the analysis was performed using CD3−CD4− gating; the bars display the representative results from dot plots. C, Relative expression of Foxp3 and Gata3 was determined in livers from WT (white bars) and Il17ra−/− (black bars) mice via real-time quantitative polymerase chain reaction and normalized to constitutive Hprt expression. D, Cells from the spleen and liver were harvested at 6 weeks after infection, and CD4+Foxp3+ cells were analyzed in the CD3+ gate, determined by flow cytometry. The bars display representative results from dot plots. E, Spleens were harvested from infected WT and Il10−/− mice at 4 weeks after infection, and cells were stimulated as described for panel A, followed by staining with specific antibodies against CD3, CD4, interferon γ (IFN-γ), and interleukin 17A (IL-17A). IL-17A–expressing and IFN-γ–expressing cells were analyzed in the CD3+CD4+ gate, determined by flow cytometry. F, Splenocytes from mice infected for 4 weeks were restimulated with 50 µg/mL of L. infantum antigen for 72 hours, and IL-17A was measured by enzyme-linked immunosorbent assay. G, Livers and spleens from WT and Il10−/− mice infected for 4 weeks were collected and weighed, and the parasite load was determined using a limiting dilution assay. The presented results are representative of 2 independent experiments (n = 5) and are expressed as mean values (± SD). *P < .05. Abbreviation: Ag, antigen.
IL-17A production induced by *L. infantum* antigen (Figure 5F). Strikingly, lower parasite burdens were detected in the livers and spleens from *Il10*−/− mice (Figure 5G), demonstrating that the development of an IL-17A–dominant response during *L. infantum* infection may block IL-10–mediated regulation and contribute to parasite restriction.

**IL-17A and IFN-γ Synergistically Promote Parasite Killing**

Because potentiated development of the Th1 and Th17 responses was observed when IL-10 was abolished and both of these cell populations participate in host defense against infection, we investigated whether IL-17A acts synergistically with IFN-γ to restrain parasite growth. We observed significant downregulation of *Ifng*, *Tbet*, and *iNOS* mRNA (Figure 6A), and the level of *iNOS* enzyme was also reduced in liver sections from *Il17ra*−/− mice (Figure 6B). Further, the expansion of CD4+ T cells producing IFN-γ was also affected in the absence of IL-17RA (Figure 6C and 6D). Together, these data demonstrate that, in contrast to WT mice, infection of *Il17ra*−/− mice leads to the generation of a Treg/IL-10–dominated response and an impaired Th1 profile, resulting in parasite growth. To investigate the mechanism by which IL-17A contributes to the Th1 response and to parasite restriction, we evaluated the microbicidal activity of infected macrophages cultured with different concentrations of rIL-17A in the presence or absence of rIFN-γ and assessed NO production and parasite killing. Using 100 ng/mL of rIFN-γ, we detected an average of 38 412 µM of nitrite in the supernatant. The addition of 300 ng/mL of rIL-17A...
plus 100 ng/mL of rIFN-γ increased 52.06% of the nitrite concentration. Moreover, the increase in NO production induced by rIL-17A exerted a significant impact on the leishmanicidal ability of the macrophages because the combination rIL-17A plus rIFN-γ significantly decreased the percentage of infected cells; this effect was observed with either 10 ng/mL (data not pictured) or 100 ng/mL of rIFN-γ (Figure 7B). Moreover, the number of parasites inside the macrophages was significantly reduced after rIFN-γ plus rIL-17A stimulation, compared with stimulation with rIFN-γ alone (Figure 7C). Corroborating these findings, we observed that, under the same conditions, more Il17ra<sup>−/−</sup> macrophages were infected than WT macrophages (Figure 7D). These results indicate that IFN-γ and IL-17A operate synergistically to activate macrophages, induce NO production, and promote parasite clearance.

**DISCUSSION**

In this study, we identified IL-17A as an important mediator of resistance against *L. infantum* infection and demonstrated that it acts synergistically with IFN-γ to promote parasite killing. We showed that *L. infantum* infection results in IL-17A production during the active phase of disease in patients and in mice. In addition, our data demonstrated the crucial role of IL-17 in conferring protection against *L. infantum* infection because Il17ra<sup>−/−</sup> mice failed to control the parasite from weeks 1 to 8.
after infection, suggesting that IL-17 plays a role in innate and adaptive immune responses. These data are consistent with previously reported findings, which demonstrated that the expansion of IL-17–producing CD4+ cells promotes self-healing in *L. braziliensis*–infected mice [24] and that the treatment of *L. donovani*–infected mice with curdlan, which induces IL-17, exerts an antileishmanial effect [25]. Moreover, IL-17 is also induced during infections with other Trypanosomatidae parasites, such as *T. cruzi*, and plays a central role in regulating parasite-induced myocarditis [16]. In addition, reduced production of IL-17 is correlated with Chagas disease severity in humans [26, 27].

The *Il17ra−/−* mice exhibited restrained inflammation as compared to the diffuse inflammatory infiltration observed in WT mice. This difference could occur because in the absence of IL-17RA, the expression of several chemokines that recruit neutrophils, macrophages, and lymphocytes is impaired [28–30]. In this context, we demonstrated that reduced mRNA expression of lymphocyte-attracting chemokines and their receptors (ie, Cxcl10, Ccl4, Cxcr3, and Ccr5) occurs in *Il17ra−/−* mice, leading to deficient accumulation of lymphocytes in inflammatory foci [31]. Despite this finding, *Cell7* and *Ccr4* mRNA were overexpressed in *Il17ra−/−* mice, favoring the accumulation of Foxp3+ and IL-10+ cells in the tissue [32, 33]. It is important to note that IL-10 production is closely related to disease exacerbation and host susceptibility [34, 35] because IL-10 inhibits lymphocyte proliferation and macrophage activation [9, 10]. The upregulation of IL-10 observed in the *Il17ra−/−* infected mice may contribute to the reduced inflammation and higher susceptibility observed in those animals. Indeed, in the absence of IL-10, IL-17 mediates pathology during *L. major* infection [36].

The role of Tregs during visceral leishmaniasis is controversial; however, because Tregs are an important source of IL-10, these cells could contribute to the chronicity of *L. infantum* infection. Previous studies demonstrated that infection with *L. infantum* induces the accumulation of CD4+CD25+Foxp3+ cells in the spleens and lymph nodes of mice [37]. In addition to the regulation of IL-10 by IL-17, we provided experimental evidence that demonstrates that IL-10 also regulates the production of IL-17A, because *Il10−/−* infected mice upregulated IL-17A production. This finding corroborates the fact that the generation of an IL-17A–producer pattern per se negatively regulates the generation of an antiinflammatory profile.

An important aspect of our findings is that IL-17 can positively modulate IFN-γ–expressing CD4+ T-cell responses. The importance of IFN-γ and Th1 responses for host resistance to intracellular pathogens is well defined [38, 39]. Assessments of the cellular mechanism by which IL-17 promotes protection led us to investigate the role of this cytokine in infected macrophages because these cells have the ability to kill *Leishmania* parasites. Dendritic cells and macrophages express significant amounts of *Il17ra* mRNA and are able to respond to an IL-17 stimulus [40, 41]. Here, we demonstrated that IL-17A works synergistically with IFN-γ to trigger the NO production by infected macrophages and promote parasite killing. A requirement for IL-17 in the assembly of a Th1 response was also described in a model of *Francisella tularensis* infection [40]. Moreover, previous reports demonstrated that IL-17 increases NO levels and the expression of iNOS in human keratinocytes [42] and that IL-17 treatment increases macrophage capacity to kill *Bordetella pertussis* [43]. In addition, splenocytes from *L. donovani*–infected mice exhibit increased IFN-γ and NO production after rIL-17 or rIL-23 treatment [25]. Because IL-17RA deficiency also affects IL-17F and IL-17E signaling [44], we cannot exclude the role of these cytokines in the protection against *L. infantum* infection. However, as IL-17F and IL-17E do not induce NO production or mediate Th1 response [40], it is reasonable to consider that IL-17A plays the pivotal role on the results presented here.

During infectious diseases, hosts can defend themselves in 2 ways: by inducing high inflammation that completely eliminates the pathogen or by maintaining the microorganisms at a number that does not cause damage [45]. In this study, we demonstrated that patients with visceral leishmaniasis produce IL-17A and that this cytokine could be associated with hepatosplenomegaly. However, IL-17 also generates the inflammatory response that is required to contain the parasite load and therefore exerts a positive effect on host resistance. In summary, we demonstrated that *L. infantum* infection induces IL-17A that modulates the inflammatory microenvironment via the down-modulation of regulatory mechanisms and sustains IFN-γ production by Th1 cells at sites of inflammation. Further, we demonstrated the elegant ability of IL-17A to work synergistically with IFN-γ to induce macrophage activation, which increases NO production and promotes parasite killing. Based on these data, we conclude that IL-17 plays an effect in the control of *L. infantum* growth.

Considering the increasing reports of visceral leishmaniasis treatment failure, it is reasonable to propose a therapy combining the clinically well-tolerated drug treatment with low doses of IL-17A to increase the leishmanicidal effect. In some cases, the inhibition of IL-17A could be also tested to prevent tissue damage. In addition, these data indicate that vaccine design should consider that the mixture of antigen/adjuvant can lead to an increase of IL-17 secretion.

**Supplementary Data**

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
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Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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