Research Article

**Taenia crassiceps Infection Attenuates Multiple Low-Dose Streptozotocin-Induced Diabetes**

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*Taenia crassiceps*, like other helminths, can exert regulatory effects on the immune system of its host. This study investigates the effect of chronic *T. crassiceps* infection on the outcome of Multiple Low Dose Streptozotocin-Induced Diabetes (MLDS). Healthy or previously *T. crassiceps*-infected mice received MLDS and type 1 diabetes (T1D) symptoms were evaluated for 6 weeks following the induction of MLDS. *T. crassiceps*-infected mice displayed lower blood glucose levels throughout the study. A significantly lower percentage of *T. crassiceps*-infected mice (40%) developed T1D compared to the uninfected group (100%). Insulitis was remarkably absent in *T. crassiceps*-infected mice, which had normal pancreatic insulin content, whereas uninfected mice showed a dramatic reduction in pancreatic insulin. Infected mice that received MLDS did not show an increase in their regulatory T cell population, however, they had a greater number of alternatively activated macrophages, higher levels of the cytokine IL-4, and lower levels of TNF-α. Therefore, infection with *T. crassiceps* causes an immunomodulation that modifies the incidence and development of MLDS-induced autoimmune diabetes.

1. Introduction

Parasitic helminths are a highly diverse group of organisms that display different morphologies, accessory structures, sexual and feeding behaviors and life cycle stages. Helminths distribute themselves across a variety of niches inside their hosts where they can cause a multiplicity of diseases. Helminth parasites also appear to follow varied and complicated oral and cutaneous routes of infection within host tissues. Surprisingly, despite these differences in features and behavior, helminths share a unique ability to exert profound regulatory effects on the immune systems of their hosts. One of the first observations made concerning helminth infection was the elicitation of a strong Th2-biased immune response [1, 2]. In the last few years, new regulatory has been identified to play a role in helminth infection [2, 3]. One of these mechanisms includes the induction of regulatory T cells (Tregs), which are now known to be involved in pathogen susceptibility and the control of inflammation in helminth infections caused by *Litomosoides sigmodontis* [4], *Trichuris muris* [5], *Brugia malayi* [6], *Trichinella spiralis* [7], and *Heligmosomoides polygyrus* [8]. Dendritic cells (DCs) have also been reported to be affected by helminth-derived products [3, 9] and, more recently, a new population of macrophages called alternatively activated macrophages (AAMsφ) has been consistently observed in several worm infection models [10, 11].

There are a series of epidemiological and experimental studies supporting the idea that helminth infections can induce a protective effect against the development of both autoimmune and allergic diseases [12]. The “hygiene hypothesis” was the first to suggest that the increase in the prevalence of allergies and asthma in developed countries might be linked to the reduction in infections with parasitic and bacterial pathogens. Thus, parasitic infection might somehow “educate” the immune system to avoid exacerbated
inflammatory responses [13, 14]. Type 1 diabetes (T1D) is an autoimmune disease that has increased in prevalence over the last several years in developed countries and is caused by the selective destruction of insulin-producing β cells located in pancreatic Langerhans' islets by autoantigen-reactive inflammatory T cells. When the majority of β cells are destroyed, the pancreas' ability to secrete insulin in response to blood glucose levels is impaired, resulting in a disruption of glucose homeostasis. Previous studies have shown that the MLDS-induced diabetes model is a useful tool for understanding the basic mechanisms associated with the origin and modulation of induced T1D. T1D has been correlated predominantly with genetic background as well as proinflammatory cytokine profiles for TNF-α, IL-12 and IFN-γ [15, 16]. For example, C57BL/6 mice are more susceptible to developing MLDS-induced T1D than mice lacking STAT-4, a transcription factor that is essential for IL-12 signaling. STAT-4 deficient mice have a delayed onset of MLDS-induced T1D and show a milder form of the disease [17].

_Taenia crassiceps_ is a cestode parasite that is useful in infection model systems for cysticercosis [18]. Infection of inbred mice with _T. crassiceps_ induces a strong Th2-like immune response that is similar to the response elicited by infection with other helminths [19]. In addition to this Th2-like response, _T. crassiceps_ infection is associated with a series of immunomodulatory events including the induction of AAMφ [20] and the inhibition of T cell proliferative responses to bystander and polyclonal stimuli [2]. We and others have found that infection with _T. crassiceps_ alters the immune response to and susceptibility to concomitant pathogens such as _Trypanosoma cruzi_ [21], vaccinia virus [22], or _Leishmania_ [18], and also reduces the efficacy of vaccination [23]. Thus, it is clear that _T. crassiceps_ infection is able to modify immune responses to concomitant pathogens.

The purpose of this study is to determine whether the immune modulation that is induced by _T. crassiceps_ infection might affect the outcome of Multiple Low Dose Streptozotocin-Induced Diabetes (MLDS). To address this question, we compared the course of MLDS development in both healthy and _T. crassiceps_-infected mice. Our data suggest that _T. crassiceps_ infection might modify the incidence and development of MLDS-induced autoimmune diabetes.

2. Materials and Methods

2.1. Mice. Six- to eight-week-old male BALB/cAnN mice and C57BL/6N Hsd mice were purchased from Harlan Laboratories (México) and were maintained in a pathogen-free environment at the FES-Iztacala, U.N.A.M. animal facility in accordance with institutional and national guidelines.

2.2. Parasites and Infection Protocols. Metacestodes of _Taenia crassiceps_ (ORF) were harvested in sterile conditions from the peritoneal cavity of female BALB/c mice after 2–4 months of infection. The cysticerci were washed four times in phosphate-buffered saline (PBS; 0.15 M NaCl, 0.01 M sodium phosphate buffer, pH 7.2) and used for mouse infection. Male BALB/c and C57BL/6 mice were infected with an intraperitoneal (i.p.) injection of 20 small, nonbudding cysticerci of _T. crassiceps_ resuspended in 0.3 mL of PBS.

2.3. Multiple Low-Dose Streptozotocin-Induced Diabetes (MLDS). Mice infected with _T. crassiceps_ for 6 weeks or uninfected controls received daily intraperitoneal injections of 40 mg/kg streptozotocin (Sigma-Aldrich; dissolved in 0.1 M sodium citrate, pH 4.5) for 5 consecutive days. Blood glucose was measured in animals that were fasted for 6 hours by an Accu-chek Advantage glucometer (Roche Diagnostics) once per week over a 6-week period. Untreated mice were included as controls. Animals were considered diabetic when fasting blood glucose was greater than means ±2 SD on two consecutive tests.

2.4. Intraperitoneal Glucose Tolerance Test. Uninfected and _T. crassiceps_-infected mice were subjected to an intraperitoneal glucose tolerance test in order to establish the effects of the MLDS-induced diabetes model on glucose metabolism (n = 6–10 for each group). Uninfected and infected MLDS-treated mice were fasted for 6 hours prior to sample collection. A basal blood sample (0 min) was collected by tail-snip and plasma glucose was evaluated using an Accu-check Advantage glucometer. Mice were then injected i.p. with filtered d-glucose (1.5 mg/kg). Glucose levels were evaluated again at 30-, 60-, and 120-minute time points.

2.5. Histology. Pancreata from C57Bl/6 and BALB/c mice were collected 6 weeks after the induction of diabetes. Tissue was processed and embedded in paraffin, and 5-μm sections were cut for histological analysis. Thin sections were stained with hematoxylin–eosin and evaluated microscopically for the presence of insulitis using the following scoring system: grade 0, normal; grade 1, minor peri-islet cell infiltration; grade 2, moderate infiltration (<50% of islet area); grade 3, severe infiltration (>50% of islet area) with damage to islet architecture.

2.6. Immunohistochemistry. Immunoperoxidase staining was performed on 5-μm paraffin sections using an avidin-biotin complex system, the Insulin Ab-6 (INS04 + INS05) mouse monoclonal antibody, and the commercial kit Dako EnVision + System-HRP (DAB). Sections were counterstained with hematoxylin. Images were captured using AxioVision Rel 4.6An and an AxioCam ICc3 connected to a Zeiss Microscope recorded the images.

2.7. Cytokine ELISAs. Peripheral blood was collected from tail snips once a week over a 6-week period. Serum IL-4 and TNF-α levels were measured by sandwich ELISA using commercial kits purchased from Peprotech (Rocky Hill, NJ, USA).

2.8. Isolation of Peritoneal Macrophages. BALB/c and C57BL/6 mice were sacrificed 6 weeks after induction diabetes. Peritoneal exudate cells (PECs) from mice STZ, STZ/Tc, and
Normal mice were obtained using 5 mL of ice-cold sterile PBS and the red blood cells were lysed by resuspending the cells in Boyle’s solution. Following two washes, the viable cells were counted by trypan blue exclusion with a Neubauer hemocytometer. PECs were adjusted to 5 × 10^6/mL in RPMI medium and then cultured in six-well plates (Costar, Cambridge, Mass). After 2 hours at 37°C and in 5% CO₂, nonadherent cells were removed by washing them with warm supplemented RPMI medium. Peritoneal macrophages were aseptically removed and processed for RNA extraction using the TRIzol reagent (Invitrogen, Carlsbad, CA).

2.9. Analysis of Cell Surface Markers in Macrophages. The Fc receptors on peritoneal macrophages were blocked with anti-mouse CD16/CD32 (Biolegend, CA, USA) and then stained with an APC-conjugated monoclonal antibody against F4/80 (Biolegend, CA, USA), PE-conjugated antibodies against PD-L1 and PD-L2, FITC-conjugated antibodies against CD23, or Alexafluor-conjugated antimannose receptor antibody (all obtained from Biolegend). The stained cells were analyzed on a FACsCalibur flow cytometer using Cell Quest software (Becton Dickinson).

2.10. T-Reg Cells Detection. Limph nodes were macerated individually using frosted glass slides. The staining Treg cells were according to the manufacturer instruction (Mouse Treg Flow Kit, Biolegend).

2.11. Reverse Transcriptase-PCR. Total RNA was extracted from purified peritoneal macrophages obtained from BALB/c and C57BL/6. mRNA transcripts in peritoneal macrophages was determined by reverse transcription (RT)-PCR. The RNA was quantified and 3 mg of RNA were reverse transcribed using the Superscript II First Strand Synthesis Kit (Invitrogen) and an oligo dT primer, as recommended by the manufacturer. Once cDNA was obtained, conventional PCR was performed. The PCR reactions contained (in a 25 mL final volume) 5 × PCR buffer blue, 10 mM dNTP, 40 nM each forward and reverse primer, 1 unit of Taq DNA polymerase (Saccate Biotechnologies, Italy), and 2 mL of the cDNA. The program used for the amplification of each gene was an initial denaturation at 95 °C for 5 minutes, 35 cycles of 95 °C for 40 seconds, the indicated melting temperature for 50 seconds and 72 °C for 40 seconds and a final extension step of 72 °C for 4 minutes. All reactions were carried out in a thermal cycler (Corbett Research, Australia). Finally, to observe the amplified products, a 1.5% agarose gel was prepared and samples were loaded with blue juice buffer containing SYBR Green (Invitrogen). The gels were visualized using a Fujifilm FLA 5000 scanner (Fuji, Japan) with FLA 5000 image reader V2.1 software to capture the shown images.

2.12. Statistical Analysis. One-tail Student t-test (glycemia, cytokine, and glucose tolerance test) was applied. P < .05 was considered statistically significant.

3. Results

3.1. Taenia crassiceps Infection Modulates Hyperglycemia and Diabetes Incidence by Multiple Low Dose Streptozotocin-Induced Diabetes. This study investigates whether T. crassiceps infection modifies the onset and development of MLDS-induced diabetes. Six weeks after infection with T. crassiceps, male BALB/c and C57BL/6 mice received MLDS (40 mg/kg) for 5 consecutive days. Blood glucose levels were analyzed each week for six weeks following the treatment with MLDS. Uninfected BALB/c mice became hyperglycemic one week post-MLDS injection (Figure 1(a)). By the second week following the induction of diabetes 100% of the uninfected mice were diabetic and remained diabetic until the end of the experimental period. In contrast, T. crassiceps-infected BALB/c mice displayed significantly lower blood glucose levels throughout the six-week period following MLDS injection compared to uninfected mice (Figure 1(a)). Interestingly, the onset of diabetes (as determined by glucose levels) was also different between uninfected and T. crassiceps-infected mice. The onset of diabetes in T. crassiceps-infected BALB/c mice occurred 2 weeks after MLDS induction; whereas the onset of diabetes occurred within the first week following MLDS induction in uninfected mice. Additionally, only 40% of T. crassiceps-infected mice developed hyperglycemia compared to 100% in uninfected mice (Figure 1(b); P < .05). Interestingly, T. crassiceps-infected mice had normal glucose tolerance test values (Figure 1(c)). In contrast, uninfected mice could not down-modulate the hyperglycemia until 2 hours after the glucose tolerance test was administered.

A different trend was observed in C57BL/6 mice. C57BL/6 mice are known to be more susceptible to MLDS-induced diabetes [24] and are more resistant to T. crassiceps infection [25, 26]. C57BL/6 mice developed higher levels of hyperglycemia than BALB/c mice, but these high glucose levels were controlled after 4 weeks by T. crassiceps infection (Figure 2(a)). Shortly after MLDS-induction, 80% of T. crassiceps-infected C57BL/6 mice were diabetic (Figure 2(b)). However, by 4 weeks following MLDS-induction infected C57BL/6 mice began to recover from the hyperglycemia. Only 20% of T. crassiceps-infected C57BL/6 mice were diabetic at the end of this experiment. MLDS treatment caused significant elevations in glucose levels during an intraperitoneal glucose tolerance test in uninfected mice, but mice carrying T. crassiceps displayed normal glucose tolerance test values (Figure 2(c)).

3.2. Lack of Insulitis in T. crassiceps Infected Mice Treated with MLDS. It is known that MLDS stimulates the recruitment of leukocytes to pancreatic islets, resulting in insulitis [15]. Pancreata were harvested at the end of the 6-week experimental period for histopathological analysis. Figure 3 illustrates islet histopathology and the development of insulitis in uninfected and T. crassiceps-infected BALB/c and C57BL/6 mice. A significant number of infiltrating leukocytes and the presence of insulitis was observed in the pancreata from uninfected mice (Figures 3(a) and 3(b)), which was associated with loss of islet architecture in some cases. Conversely,
Figure 1: Hyperglycemia and diabetes incidence is modified by *T. crassiceps* infection in BALB/c mice. (a) Blood glucose levels throughout the MLDS protocol for uninfected BALB/c mice and BALB/c mice infected with *T. crassiceps* for 6 weeks. (b) Percent incidence of diabetes between uninfected and *T. crassiceps*-infected BALB/c mice. (c) Intraperitoneal glucose tolerance test for MLDS-treated uninfected and *T. crassiceps*-infected mice. Dotted line indicates normal glucose values. *P < .05, n = 12.

The islet histopathology from *T. crassiceps*-infected mice was devoid of both cellular infiltrates and insulitis (Figures 3(a) and 3(b)). Similar results were observed in the pancreata from BALB/c and C57BL/6 mice.

### 3.3. Immunohistochemistry of Insulin in MLDS-Treated Mice

To determine whether islet cells from either uninfected or *T. crassiceps*-infected mice are able to produce insulin, we performed specific immunostaining of pancreatic tissue using an anti-insulin antibody. MLDS-treated *T. crassiceps* infected mice demonstrated strong insulin staining in their pancreatic islets as compared with normal (untreated and uninfected) mice (Figure 4(a)). In contrast, MLDS-treated uninfected mice had weak insulin staining, suggesting a substantial loss of insulin granules in islet β-cells. A similar result was obtained from C57BL/6 mouse tissues (Figure 4(b)).

### 3.4. *T. crassiceps* Infection Increases IL-4 Levels in MLDS-Treated Mice

To analyze whether the inhibition of diabetes in helminth-infected MLDS-treated mice was due to an alteration in the Th1/Th2 balance, cytokine levels from the sera of uninfected and infected mice were measured. The Th1-associated cytokines IFN-γ and TNF-α have been reported to accompany the development of diabetes in both NOD and MLDS-induced mouse models [14, 27]. While BALB/c mice did not show significant changes in TNF-α levels in response
to MLDS treatment (Figure 5(a)), uninfected C57BL/6J mice had high levels of TNF-α and IFN-γ in their sera (Figure 5(c), and data not shown). Interestingly, C57BL/6 mice that were previously infected with T. crassiceps and then treated with MLDS displayed lower sera TNF-α levels but maintained elevated levels of IFN-γ, as compared to uninfected mice (data not shown). We also evaluated the effect of T. crassiceps infection on the presence of the Th2-associated cytokine IL-4. At some experimental time points, IL-4 levels were significantly enhanced in both T. crassiceps-infected BALB/c and C57BL/6 mice that received MLDS whereas uninfected mice with T1D had lower levels of serum IL-4 (Figures 5(c) and 5(d)).

3.5. Presence of AAMφ, but Not Tregs, in MLDS-Treated T. crassiceps-Infected Mice. In the last few years, new classes of regulatory cells that are induced by helminth infections have been identified. Tregs and AAMφ have been implicated in the control of immune pathology associated with helminth infection, but both cell types have also been associated with suppression of the immune response [28, 29]. In order to determine whether these cells play a role in T. crassiceps-mediated diabetes prevention, we performed FACS analysis of peritoneal cells and T cells from the mesenteric lymph node. Following MLDS treatment, neither uninfected nor T.
crassiceps-infected mice displayed an increase in the population of Treg in the mesenteric lymph node (Figure 6(a)). Interestingly, T. crassiceps-infected mice displayed an increase in the percentage of AAMφ in the peritoneum, as determined by the expression of the mannose receptor, CD23, PDL1, and MHCII (Figure 6(b)). To confirm the presence of AAMφ, RT-PCR was performed to detect mRNA transcripts for Fizz-1 and PDL-1. These transcripts were present in peritoneal cells from T. crassiceps-infected mice treated with MLDS, but not in uninfected, MLDS-treated mice (Figure 6(c)).
4. Discussion

*T. crassiceps* infection and its associated antigens can induce Th2-type responses in vivo [20] and can modulate the immune response to bystander antigens or live infections [2]. *T. crassiceps*, like other helminth parasites, has the ability to manipulate and down-modulate the immune responses of its hosts [10, 18]. It is widely accepted that the initiation and development of T1D is mainly caused by an autoimmune cell-mediated destruction of β cells in the pancreas [15]. Genetic, immunological, and environmental factors can also influence the onset and development of T1D [30].

In this study, we found that *T. crassiceps* infection could alter the development of MLDS-induced diabetes in mice. This study demonstrates that *T. crassiceps*-infected mice develop a mild, and sometimes transient, form of T1D after MLDS treatment. In contrast, uninfected mice exhibited an accelerated, more severe form of T1D.

There are likely several factors that contribute to the protection by *T. crassiceps* infection against MLDS-induced diabetes. First, the prominent Th2 environment that is induced by *T. crassiceps* infection [19, 31] might counteract the proinflammatory responses that are necessary to generate complete MLDS-induced diabetes. Second, *T. crassiceps* infection might alter T cell recruitment to the pancreas. Third, *T. crassiceps* infection might induce a regulatory cell response that dampens inflammatory processes during MLDS-induced diabetes.

The findings of this study demonstrate that infection with *T. crassiceps* maintains high levels of IL-4 and that there is a slight reduction in serum TNF-α levels after infected mice are treated with MLDS. TNF-α has been implicated as a critical player in leukocyte-mediated islet damage [32]. Thus, this type of immune regulation might be responsible for the decrease in pathology and lower incidence of T1D observed in *T. crassiceps*-infected mice. Consistent with a putative protective role for Th2 type cytokines (IL-4), NOD mice that express IL-4 in their pancreatic β cells are protected from insulitis and autoimmune diabetes [33]. Other experimental models have demonstrated that helminth exposure (*Schistosoma mansoni*, *Trichinella spiralis*, *Hymenolepis diminuta* or *Heligmosomoides polygyrus*) to mice might drastically reduce the symptoms of autoimmune diseases such as Inflammatory Bowel Disease (IBD), Encephalomyelitis Autoimmune Experimental, and T1D, mainly by reducing IL-12 and IFN-γ production and enhancing IL-4 and IL-10 levels [34–45]. Female NOD mice that spontaneously develop diabetes due to Th1-mediated destruction of pancreatic β-cells are protected from developing diabetes when they are exposed to *S. mansoni* [34–36], and IL-4 has been shown to play an important role in this protection [46, 47]. It will be necessary to test our system in mice that either lack IL-4 or have been treated with a specific IL-4 inhibitor to fully understand the role that IL-4 plays in *T. crassiceps* protection against MLDS-induced diabetes.
We found that *T. crassiceps* infection resulted in an increase in the population of F4/80+ macrophages that express CD23, PDL1, MR, Arg1, Ym1, but not iNOS, an expression profile that is now used to identify AAMϕ. AAMϕ might function as bystander suppressors of the immune response. Alternatively, they might inhibit cell infiltration in the pancreas, given their established suppressive activity, which is mediated through cell-contact, where PD-L1 and PD-L2 play a preponderant role, or by releasing soluble factors [20]. In contrast, Treg cells were not detected in *T. crassiceps*-infected mice. Mice that were infected with *T. crassiceps* were protected from both hyperglycemia and lymphocyte infiltration into the pancreatic islet despite the absence of regulatory T cells. This is interesting given the recent findings that demonstrate the importance of Foxp3+ regulatory T cell expansion in mice infected with helminths [4–8]. Tregs induced by *S. mansoni* and its associated antigens have been implicated in diabetes prevention in NOD mice [36]. This discrepancy might be explained by differences in the classes of helminths used in these infection models, in the route of infection used, or by different suppressive mechanisms that are turned on by *T. crassiceps* versus *S. mansoni* [11, 19]. Only one published report demonstrates that macrophages are involved in preventing the pathology associated with IBD model [48]. Therefore, it is possible that AAMϕ might actively participate in dampening the pathology associated with MLDS-induced diabetes, perhaps by the known ability of AAMϕ to strongly suppress T cell responses.

Interestingly, MLDS-induced diabetes is associated with Th1-type responses [17] and C57BL/6 mice show a Th1-type response in the MLDS model [24]. We also show that *T. crassiceps*-infected C57BL/6 mice demonstrated a reversal of MLDS-induced diabetes even though they were more hyperglycemic at earlier time points following MLDS-treatment. Again, the specific regulatory cells and/or cytokines involved in these protective effects still need to be identified, however, according to our data, appears that AAMϕ it may have an
Figure 6: Flow cytometry analysis for the detection of regulatory T cells and alternatively activated macrophages. (a) Mesenteric lymph nodes from BALB/c mice were processed and cells were staining for Treg cell detection with anti-CD4, CD25, and Foxp3 (Tregs kit, Biolegend). (b) Peritoneal exudates cells stained with conjugated anti-F4/80, CD23, MR, PDL1, and MHCII and analyzed by flow cytometry. (c) RT-PCR analysis of PDL-1, RELM-α, and GAPDH in macrophages from uninfected and T. crassiceps-infected BALB/c mice.
important role instead T-regulatory cells that we could not detect in *T. crassiceps*-infected mice.

5. Conclusion

Our data support the notion that the protection from autoimmunity by helminth infection could be attributed to immunoregulatory mechanisms triggered by these parasites. Our study demonstrates for the first time that *T. crassiceps* infection protects against Multiple Low Dose Streptozotocin-Induced Diabetes, independently of the genetic background of the host. Furthermore, we present a possible protective role for AAMs since we did not detect enhanced Treg cells. The analysis of *Taenia*-released products and repeating our experiments under conditions of macrophage depletion will be necessary to fully understand the mechanisms involved in this observed protection.

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