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Depressed T-Cell Proliferation Associated with Susceptibility to Experimental *Taenia crassiceps* Infection

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Peritoneal infection with *Taenia crassiceps* cysticerci of naturally resistant (C57BL/10J and C57BL/6J) and susceptible (BALB/cAnN) mice induces a cellular immune depression. T-cell proliferation in response to concanavalin A (ConA) or anti-CD3 was significantly depressed in infected mice of all strains tested. However, in resistant mice, the diminished response to ConA was transient and animals recovered normal responsiveness at day 40, whereas susceptible mice remained suppressed throughout the 40 days of the experiment. In contrast, the proliferative response to anti-CD3 was lower in infected mice than in noninfected controls regardless of differences in natural susceptibility of the strains. Intraperitoneal injection of mice with a parasite extract also induced a depression of the response to ConA, although not as strong as that produced by the parasite itself. This depression is not due to direct effects by parasite antigens over host lymphocytes, as proliferation is not affected by the presence of cysticercal antigens added in vitro. Diminished interleukin-2 production during the parasitosis accounts at least in part for the diminished responses to ConA. A primary infection favors parasite establishment after a second challenge, pointing to the relevance of the immunodepression in generating a host environment favorable to the parasite.

Taenia crassiceps cysticerci cause a chronic infection in laboratory animals such as mice (10, 27) and rats (5). Cysticerci grow in the peritoneal cavity, where they reproduce by budding and from where they can be harvested and individually counted to estimate how susceptible different strains are. Host susceptibility and the intensity of this murine cysticercosis depend on a combination of genetic (24), sexual (6, 13, 24), and anatomical (19) factors. In addition, survival and growth of the cysticerci within the host probably involve mechanisms of immune response evasion as occurs in other parasitosis (29). Thus, *T. crassiceps* peritoneal infection induces a concomitant decline in antibody response against sheep erythrocytes (12) and inhibits mast cell degranulation (26). However, the importance of these immune response modifications in the establishment and persistence of cysticerci within the host remains uncertain. In an attempt to improve our understanding of the role of immunity in experimental cysticercosis, we undertook a study of immune functions of infected animals from strains differing in natural resistance to this parasite. In this report, we describe the appearance of cellular immune depression in *T. crassiceps*-infected mice as evidenced by a diminished lymphocyte proliferation, attributable at least in part to an insufficient supply of endogenously produced interleukin-2 (IL-2). Furthermore, our results point to the relevance of immune depression in the establishment and/or growth of parasites within the host.

MATERIALS AND METHODS

Mice. Three strains of mice differing in susceptibility to *T. crassiceps* were used: C57BL/10J and C57BL/6J (resistant) and BALB/cAnN (susceptible). Original stocks were obtained from the Jackson Laboratory, Bar Harbor, Maine, and from M. Bevan (Seattle University), respectively, and then bred in our animal facilities by brother-sister mating. All mice used were 5 to 7 weeks old at the start of the experiments. The experiments reported herein were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council, Washington, D.C.

Parasites. The ORF strain of *T. crassiceps* (Zeder 1800) Rudolphi 1810, isolated by Freeman (10) and supplied by B. Enders (Behringwerke, Marburg, Germany), has been maintained by serial intraperitoneal passage in BALB/cAnN female mice for 8 years in our institute. Parasites for infection were harvested from the peritoneal cavity of mice 1 to 3 months after inoculation of 10 cysticerci per animal.

Infections and immunizations. Mice were routinely injected intraperitoneally with 10 small (2 mm in diameter), nonbudding *T. crassiceps* larvae suspended in phosphate-buffered saline (PBS). Either 5, 12, 30, or 40 days after infection, mice were sacrificed, their spleens were removed for proliferation assays, and *T. crassiceps* cysts inside the peritoneal cavity were counted. For some experiments, mice were inoculated intraperitoneally with 100 μg of a mixture of soluble *T. crassiceps* antigens in PBS, prepared as previously reported (18).

Proliferation inducers. Concanavalin A (ConA), obtained from Sigma Chemical Co. (St. Louis, Mo.), was prepared as previously described (8). IL-2-rich supernatant from the 929 cell line (IL-2-transfected fibroblasts) was kindly provided by José Moreno (Hospital de Especialidades, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico). Anti-CD3 antibodies from hybridoma 145.2C11 were prepared as described previously (21).

Proliferation assay. Spleen cells from normal, immunized, or parasitized mice were cultured in RPMI 1640 medium supplemented with L-glutamine (0.2 mM), sodium pyruvate (1 mM), nonessential amino acids (0.01 mM), penicillin (100 U/ml), streptomycin (100 μg/ml), and fetal calf serum (10%). Cells were incubated with the appropriate concentrations of ConA or anti-CD3 at 37°C in a 5% CO_2 humidified atmosphere, in flat-bottom microtiter plates, at a concentration of 5×10^5 cells per 200-μl final volume. After 48 h, cells were pulsed (1 μCi per well) for a further 18 h with [^{3}H]thymidine ([^{3}H]TdR; New Products, Du Pont, Boston, Mass.). They were then harvested, and the amount of incorporated label was measured by counting in a liquid scintillation spectrometer. All assays were performed in triplicate in at least four individual mice. To test for inhibitory effects of *T. crassiceps* antigens on cell proliferation, cultures from normal mice prepared as described above were treated with 50 to 5,000 ng of soluble vesicular fluid antigens per ml added either simultaneously with ConA or 3 or 17 h later.

Effect of IL-2 on proliferation of cells from *T. crassiceps*-infected mice. IL-2 activity in the supernatant of the 929 cells was determined by measuring [^{3}H]TdR uptake by the CTLL-2 cell line as described by Gillis et al. (11); IL-2 units were calculated relative to a recombinant IL-2 (rIL-2) standard (Sigma). The effects of IL-2 on ConA-stimulated cultures from normal and 5-day-infected mice was evaluated by adding 10 to 100 U of rIL-2 per ml concomitantly with ConA.

Effect of previous immunization and a first challenge on susceptibility. The effect of a primary infection with *T. crassiceps* on the establishment of a secondary infection with the same parasite was determined as follows. C57BL/6J male

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TABLE 1. Growth of *T. crassiceps* in the peritoneal cavity of susceptible and resistant mouse strains

Mouse strain	Sex	Avg parasite load[a] (mean ± SE)
BALB/cAnN	Female	122.1 ± 8.07
	Male	30.3 ± 2.1
C57BL/6J	Female	3.07 ± 2.7
	Male	0
C57BL/10J	Female	15.8 ± 5.6
	Male	0

[a] Cysticerci recovered 30 days after infection with 10 cysticerci per mouse.

mice were infected with *T. crassiceps* as described above and 5 days later inoculated again with 10 cysticerci each. As controls, normal mice were infected once either with 10 or 20 parasites each. Cysticerci were counted after 30 days of infection.

Statistical analysis. The statistical significance of the effects of the experimental variables was determined by multifactorial analysis of variance and by the nonparametric test Wilcoxon scores (rank-sums).

RESULTS

Proliferative responses to ConA by spleen cells from resistant and susceptible mice during the course of *T. crassiceps* infection. We have reported previously that inbred strains of mice differ in susceptibility to *T. crassiceps*; the BALB/cAnN strain was among the most susceptible, whereas the C57BL/6J strain was comparatively resistant (24). Results in Table 1 show that C57BL/10J mice are also resistant to the parasite and confirm our previous finding that female mice are more susceptible than males to intraperitoneal cysticercosis (13, 24). To evaluate T-lymphocyte function during experimental infection with *T. crassiceps*, proliferative responses to ConA were determined in spleen cells from BALB/cAnN and C57BL/10J mice at different times after infection. As shown in Fig. 1, diminished proliferative responses to ConA stimulation were observed in both resistant and susceptible mice as early as 5 days after infection. This effect was more marked in the resistant C57BL/10J mice, in which a reduction of 79% with respect to control mice was observed. However, at later stages of infection (40 days), spleen cells from resistant mice recovered the ability to respond to ConA, whereas the response of cells from

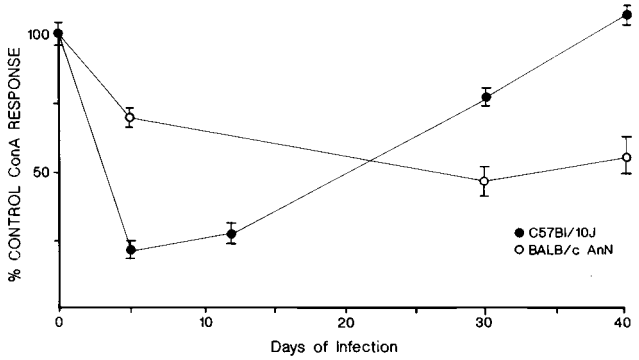

FIG. 1. Effect of *T. crassiceps* infection on ConA-induced proliferation of splenocytes from susceptible (BALB/cAnN) and resistant (C57BL/10J) mice. Data were calculated as percentage of the response of control noninfected mice. Means ± standard deviations of incorporation (in 10^3 cpm) were 265.7 ± 83.1 for control BALB/cAnN mice and 163 ± 60.7 for C57BL/10J mice. Each point represents the average response ± standard error of three to eight individual mice. The response of infected mice of both strains was significantly lower ($P < 0.01$) than that of control mice on days 5, 12, and 30. On day 40, only T-cell proliferation of susceptible BALB/cAnN mice was significantly lower.

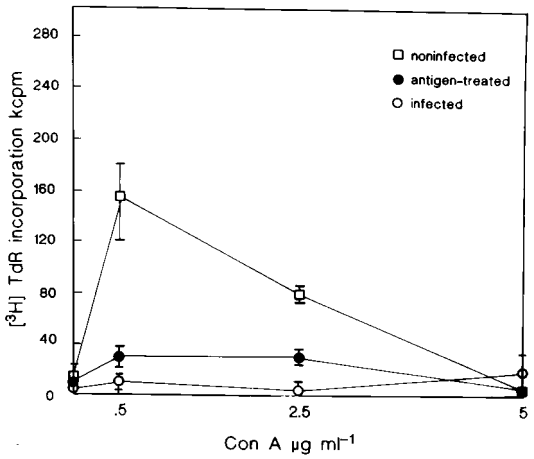

FIG. 2. ConA dose responses of spleen cells from noninfected, 5-day-infected, or immunized C57BL/10J male mice. Points and vertical bars represent the means of triplicate values and standard deviations. Immunization and infection significantly reduced the ConA responses ($P < 0.05$), with a higher significantly decrease due to the infection.

susceptible mice remained at a lower level (55%) than that of cells from uninfected mice. Similar diminished cell proliferation to ConA and kinetics was observed in *T. crassiceps*-infected C57BL/6J mice (e.g., Table 4) and in another resistant strain, B10.D2 (data not shown).

Next, we determined if the depressed responses to ConA observed in cells from infected mice could also be observed in cells from mice injected with soluble cysticercal *T. crassiceps* antigens. As shown in Fig. 2, the response of cells from infected and from antigen-treated mice was significantly lower than that of normal mice after stimulation with 0.5 and 2.5 μg of ConA per ml. However, at these ConA doses, a statistically significant lower response was observed in cells from infected mice than in those from antigen-treated mice.

To ascertain if immunodepression was also induced by *T. crassiceps* antigens in vitro, we investigated their effects on normal mouse lymphocyte proliferation. Different amounts of cysticercal antigens were added to the cultures either at the time of ConA addition or 3 or 17 h later. As Table 2 shows, proliferation of cells from normal mice cultured in the presence of *T. crassiceps* antigens was not affected at any of the concentrations tested.

T-cell activation by cross-linking of CD3 antigens. T-cell proliferation induced by anti-CD3 antibodies was also evaluated. For these experiments, spleen cells from BALB/cAnN and C57BL/6J mice that had been infected 40 days previously

TABLE 2. Lack of in vitro effect of *T. crassiceps* antigens on the capacity of normal C57BL/10J splenocytes to incorporate [^{3}H]TdR in response to stimulation with ConA

Amt of *T. crassiceps* antigens added (ng/ml)	Mean [^{3}H]TdR incorporation (10^3 cpm) ± SD[a]		
	0 h[b]	3 h	17 h
0	131.1 ± 27.8	124.2 ± 19.4	135.1 ± 34.5
50	148.5 ± 7.3	116.3 ± 62.2	131.6 ± 9.4
500	156.6 ± 7.9	124.4 ± 66.8	134.6 ± 2.1
5,000	124.4 ± 41.2	152.4 ± 12.9	189.8 ± 45.5

[a] Values for three mice per group. The differences between T-cell proliferation levels in the absence or in presence of *T. crassiceps* antigens were not statistically significant. The data are representative of three repeat experiments.
[b] Time of antigen addition after ConA.

TABLE 3. Effect of chronic *T. crassiceps* infection on ConA- or anti-CD3-induced T-cell proliferation from susceptible (BALB/cAnN) or resistant (C57BL/6J) mice

Mouse strain	Mean [^{3}H]TdR incorporation (10^3 cpm) ± SD[a]			
	ConA (0.5 μg/ml)	Anti-CD3		
		1 μl	10 μl	50 μl
BALB/cAnN				
Noninfected	324.1 ± 28.8	122.0 ± 30.7	152.8 ± 14.7	106.7 ± 17.6
Infected	179.0 ± 53.4	25.7 ± 12.4	48.9 ± 4.2	26.4 ± 2.20
C57BL/6J				
Noninfected	187.1 ± 21.2	34.0 ± 10.2	39.6 ± 3.3	34.7 ± 6.2
Infected	205.0 ± 11.2	9.0 ± 7.2	12.1 ± 3.3	16.8 ± 0.4

[a] T-cell proliferation from three individual mice per group. Mice were infected 40 days before the assay. All differences between values obtained from infected and noninfected mice stimulated with anti-CD3 were statistically significant ($P \leq 0.05$, Student t test). The data are representative of three repeat experiments.

were incubated with different amounts of supernatant containing an anti-CD3 monoclonal antibody. The results are shown in Table 3. At this stage of infection, the resistant strain C57BL/6J mice had recovered the normal responsiveness to ConA (see also Fig. 1). In contrast, the anti-CD3-induced proliferation was diminished in both strains regardless of differences in susceptibility.

Effect of exogenous rIL-2 on mitogen-induced proliferation of spleen cells from infected mice. To determine if the depressed ConA response observed in spleen cells from infected mice was due to an inadequate amount of IL-2 in the cultures and to examine if these cells were capable of responding to IL-2, we evaluated the effect of exogenously added rIL-2 on the ConA-induced proliferative response of noninfected and infected mice. As Table 4 shows, addition of IL-2 (10 to 100 U/ml) did not modify the maximal level of the ConA response in spleen cells from noninfected mice. In contrast, rIL-2 significantly increased the response to ConA in spleen cells from infected mice. However, the level of response in the presence of rIL-2 did not reach that of normal mice even when large doses of rIL-2 were used. These results indicate that the diminished responsiveness to ConA observed in spleen cells from infected mice is partially due to insufficient supply of endogenously produced IL-2.

Effect of a first infection with *T. crassiceps* cysticerci on a second challenge. To investigate if the depressed cellular response of infected mice may have a bearing on the establishment of the parasite, we analyzed the effect of a first infection as well as immunization upon a secondary challenge with the parasite, using C57BL/6J male mice. As Tables 1 and 5 show, C57BL/6J is a highly resistant strain from which no parasites could be recovered, even when mice were intraperitoneally inoculated with 20 cysticerci. However, as shown in Table 5, 33 to 46% of these mice displayed parasitosis when they were challenged with 10 parasites 5 days after a previous infection or antigen injection, a time when the maximal cellular depression is observed (Fig. 1). These results indicate that parasites as well as parasite antigens may facilitate the establishment of cysticerci upon a second challenge even in highly resistant hosts.

TABLE 4. Partial restoration by exogenous rIL-2 of the depressed ConA T-cell responses in *T. crassiceps* infection

rIL-2 added (U/ml)	Mean [^{3}H]TdR incorporation (10^3 cpm) ± SD[a]	
	Noninfected	Infected
0	187.5 ± 38.3[b]	58.86 ± 4.9[c]
10	186.9 ± 33.4[b]	54.34 ± 2.5[c]
50	212.4 ± 7.5[b]	129.63 ± 32.5[d]
100	173.8 ± 12.5[b]	105.79 ± 5.7[d]

[a] Proliferation was measured in pooled cells from three normal and three 5-day-infected C57BL/6J mice.

[b,c,d] Data labeled with the same letter are not significantly different from each other, whereas those with different letters are significantly different (ANOVA test, $P < 0.01$). The data are representative of three separate experiments.

DISCUSSION

Our results clearly show that infection with *T. crassiceps* cysticerci induces a depression of the T-cell proliferative response to ConA and to an anti-CD3 monoclonal antibody. The reduction of this response was very pronounced in both naturally susceptible and resistant mice. In susceptible mice, the depressed response to ConA appears as early as 5 days after infection and is sustained for 40 days, while in resistant mice, the depression decreases after 30 days and is no longer present at day 40 postinfection. Restoration of normal levels of ConA-induced proliferation observed 40 days after infection in resistant mice may be related to the presence of only a few parasites at this time of infection, whereas in susceptible BALB/c mice, the long-term depression may reflect that *T. crassiceps* continues to reproduce in the peritoneal cavity. Diminished anti-CD3-induced T-cell proliferation was also found, in both resistant and susceptible mice, even at late stages (40 days) of infection (Table 3). At this time, the low anti-CD3 response in resistant mice contrasts with the recovery of ConA responsiveness; and while we have no explanation for this finding, it may simply reflect differences in the mechanisms of T-cell activation by these two agents. Thus, in well-established chronic parasitosis, the T-cell response is defective, seemingly because of this low proliferation to anti-CD3 stimulation. These observations suggest that *T. crassiceps* cysticerci can develop ways to evade the host defense, allowing the establishment of a balance

TABLE 5. Effect of a primary infection or antigen treatment on susceptibility of male C57BL/6J mice to a second *T. crassiceps* challenge

First treatment, day 0	No. of larvae in a challenge, day 5	Total no. of larvae recovered, day 35 (no. of mice bearing larvae/total no. challenged)[a]
Nil	10	0 (0/15)
Nil	20	0 (0/15)
100 μg of antigen/mouse	10	7 (6/13)
10 larvae/mouse	10	27 (4/12)

[a] For statistical analysis, the nonparametric test Wilcoxon scores (rank-sums) was used.

between the host and the parasite, to the point that they coexist, and the parasite multiplies, albeit with some restraint.

Interestingly, not only living cysticerci but, to a lesser degree, also *T. crassiceps* cysticercal antigens can induce this T-cell depression as early as 5 days after injection into mice (Fig. 2). This antigen-induced depression prompted the speculation that larval products may bind to the cell surface and interfere with mitogens and antigens. However, this explanation was ruled out since no effect was observed when parasite antigens were incubated in vitro with cells and ConA (Table 2). This finding, in turn, suggests that cysticercal antigens neither damage the host's lymphocytes nor occupy or block lymphocytes receptors, at least in vitro, and strongly supports the notion that the observed depression is not a consequence of parasite components that directly affect T-cell proliferation.

Immunodepression has been observed in several parasitic infections. There are many instances of immunosuppression induced by phylogenetically unrelated parasites, with very different life cycles, and host ranges, and pathological consequences (1, 2, 3, 20). In addition, a variety of mechanisms leading to this low responsiveness have been uncovered. Thus, some infections inhibit phagocytic cell activity, decrease the production of lymphokines (4, 22, 30) or their cell receptors (4, 14), and decrease the expression of molecules necessary for T-cell activation (28). Also, the presence of T suppressor cells has been reported (15, 16, 29). Here, we have shown that the suppressed ConA response observed in cysticercosis could be attributed at least in part to defects in IL-2 production, since the addition of rIL-2 to cell cultures partially restore responsiveness. It remains to be explored if defects related to IL-2 receptor also play a role in these processes. Since unpurified splenocytes were used in these studies, we cannot rule out a possible contribution from macrophages or their products to the diminished T-cell proliferation or IL-2 secretion as has been shown in other parasitic infections (17, 20).

Recent data indicate that immunosuppression may be associated with persistence or exacerbation of some parasitic infections (29). Our evaluation of a possible role of immunodepression on the establishment of cysticerci in the host suggests that an initial infection or parasite contact (which effectively depressed T-cell proliferation) can modify the natural high resistance of a host (Table 5). Thus, after a moderate challenge, no parasite growth was observed in untreated resistant C57BL/6J mice; in contrast, a previous infection or antigen treatment allowed parasite establishment. However, since parasites were not found in all inoculated mice, other factors such as parasite heterogeneity might also be involved. This parasite growth facilitation observed early after antigen inoculation contrasts with the late effects of immunization. Mice challenged 15 or 30 days after immunization with total cysticercal antigens showed a significantly lower parasite load than did nonimmunized mice (25, 32). This finding is not surprising in view of the multiplicity of mechanisms that appear to be involved in the control of larval cestodes, and it also suggests that the timing between vaccination and challenge should be considered in the evaluation of vaccine efficacy. In this context, it should be mentioned that immunization with some cysticercal antigen fractions (205 to 220 and 108 kDa) can facilitate parasitosis, causing an increase in cysticercal load even if the challenge was given late after immunization (32). We are currently investigating if this phenomenon is the result of specific immunosuppression.

Previous studies on murine *T. crassiceps* cysticercosis revealed that cellular immune mechanisms are involved in resistance. Thus, an increase of a delayed-type hypersensitivity response to parasite antigens was found to correlate with enhanced resistance. Moreover, neonatal thymectomy significantly decreased resistance, and resistance could be restored by T-cell transfer (6). More recently, preliminary evidence of a Th1-Th2 imbalance favoring Th2 has been obtained (31). As it stands, resistance to *T. crassiceps* is more clearly associated with cellular immunity than with bulk antibodies (6), although the latter are quite conspicuous components of the host immune response, and some could be involved in subtle ways in resistance. In addition, it has been recently demonstrated that natural killer cells, through the production of gamma interferon, which induces Th1 lymphocyte differentiation, play a major role in natural resistance to intracellular parasites (7, 23). Whether natural killer or other cell types (9) are important for the control of cysticercosis is not known and should be explored.

Thus, the data in this report suggest that cysticerci are more effective than cysticercal antigens in inducing immune depression by affecting T cells, modifying their IL-2 secretion, and favoring the establishment and/or development of the parasite. Exploration of the mechanism by which *T. crassiceps* induces depression of lymphocyte functions could help not only to further the knowledge of immune mechanisms that participate in this host-parasite relationship but also to advance our understanding of the regulatory events governing lymphocyte activation.

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