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Immunodepression in *Taenia crassiceps* Infection: Restoration of the In Vitro Response to Sheep Erythrocytes by Activated Peritoneal Cells

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The in vitro response to sheep erythrocytes of mesenteric lymph node cells from mice infected with the larval cestode *Taenia crassiceps* is significantly depressed and can be restored to control levels by addition of activated peritoneal cells depleted of functional T or B lymphocytes. Adherent mesenteric lymph node cells from infected mice are unable to reconstitute the in vitro response to sheep erythrocytes of normal nonadherent cells. The responses of mesenteric lymph node cells from infected mice to the T-lymphocyte mitogens concanavalin A and phytohemagglutinin and the B-lymphocyte mitogen lipopolysaccharide are normal. Mesenteric lymph node cells from infected mice do not suppress the in vitro response to sheep erythrocytes of normal mesenteric lymph node cells. These results suggest that the immunodepression in *T. crassiceps*-infected mice is primarily the result of alterations in functional accessory cells.

Depression of the immune response of a host occurs in a number of different parasitic infections. Several mechanisms have been postulated, including antigenic competition (4, 6, 15, 28), induction of suppressor cells (2, 3, 5, 13, 15, 24), defects in accessory cell (macrophage) function (1, 11, 17, 29, 31), and interference with antigen uptake by nonspecific inflammatory processes (18). The mechanism of immunodepression is not identical in all types of parasitic infections, and it is not yet clear whether the predominating mechanism is determined by the species of parasite involved, or by other factors such as the site of infection.

Previous studies in our laboratory have shown that infection of mice with larvae of the cestode *Taenia crassiceps* results in depression of the antibody response to sheep erythrocytes (SRBC) both in vivo and in vitro (8). The depression is most consistently and dramatically demonstrated in vitro when primary responses to SRBC of mesenteric lymph node (MLN) cells from infected mice are compared with controls. The present study was undertaken to investigate the mechanism of immunodepression in *T. crassiceps* infection. Functional analysis of the cells from normal and infected mice show that the immunodepression associated with *T. crassiceps* infection is primarily due to a defect in accessory cell activity.

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MATERIALS AND METHODS

Mice. BDF_1 mice, age 2 to 4 months, were used for all experimental work. Only mice of the same sex and age were used for each individual experiment.

Parasites. *T. crassiceps* larvae of the ORF strain were maintained by serial intraperitoneal inoculation in mice. Larvae were harvested from donor mice 3 to 8 months after inoculation. Experimental mice were given 20 larvae in 0.5 ml of saline, using a tuberculin syringe and 16-gauge needle, 5 to 8 weeks before harvest of cell preparations. Control mice received only saline.

In vitro immunization. Primary suspension cultures of MLN cells were prepared as previously described (19). The culture medium was RPMI 1640 (Grand Island Biological Co., Grand Island, N.Y.) supplemented with pyruvate, L-glutamine, nonessential amino acids, 25 mM *N*-2-hydroxyethyl piperazine-*N'*-2-ethanesulfonic acid buffer, 50 U of penicillin per ml, 50 μg of streptomycin per ml (Microbiological Associates, Bethesda, Md.), 5×10^{-5} M 2-mercaptoethanol (J. T. Baker Chemical Co., Phillipsburg, N.J.), and 5% fetal bovine serum. Unless otherwise noted, cells were cultured in triplicate at 3×10^6 cells/well in a volume of 0.4 ml in tissue culture plates (Falcon Plastics, 16-mm diameter, #3008, Oxnard, Calif.). All cultures were harvested and assayed for plaque-forming cells (PFC) on day 5. Cell recoveries and viabilities (determined by trypan blue dye exclusion) from normal and infected mice were similar.

Peritoneal cells. Peritoneal cells (PCs) were obtained by injecting approximately 10 ml of sterile balanced salt solution into the peritoneal cavity of BDF_1 mice with a 10-ml syringe and an 18-gauge needle. The body cavity was gently massaged, and the cells were withdrawn 3 to 5 min later. After centrifu-

gation at 250 × g for 10 min, the cells were resuspended in complete tissue culture medium.

Preparation of adherent and nonadherent cells. The method used was a modification of the method of Mosier (21) for obtaining adherent spleen cells. Briefly, MLN cells from normal or infected mice were cultured at 3×10^6 cells/well in a volume of 0.4 ml in tissue culture plates (Falcon Plastics, 16-mm diameter, #3008) in complete medium supplemented with 5% fetal bovine serum. Cultures were incubated at 37°C for 1 to 2 h. Nonadherent cells were then transferred to new culture wells, and the remaining adherent cells were washed twice with sterile balanced salt solution–5% fetal bovine serum at 37°C. Complete tissue culture medium was added to the adherent cells, and both adherent and nonadherent cells were cultured for an additional hour. After incubation, the medium from the adherent cell cultures was used to wash the cells and was then discarded. Nonadherent cells from normal or infected mice were then added to the wells containing adherent cells from either normal or infected mice and cultured in the presence of SRBC. All cultures were harvested and assayed for PFC on day 5. The proportion of adherent cells recovered from the MLN cell preparations of normal and infected mice was similar.

Bacterial-conditioned medium. Bacterial-conditioned medium (BacCM), a potent adjuvant for inducing immunity in vitro (26), was used for stimulation of PCs. This medium, the culture supernatant from the psychrophilic gliding bacteria designated GB-1, was the gift of Stan Shiigi, Department of Bacteriology and Immunology, University of California, Berkeley.

T-cell depletion. Rabbit anti-mouse brain serum was prepared, absorbed, and tested by the procedures of Golub (7). Cells were treated with rabbit anti-mouse brain for 30 min at 4°C at a concentration of 1×10^7 cells/ml. The cells were then centrifuged (250 × g for 10 min), and the pellet was resuspended and incubated in the presence of agarose-absorbed guinea pig complement for 30 min at 37°C. Dilutions of antisera were used that killed at least 95% of a thymocyte suspension and eliminated all T-helper activity in normal spleen as shown by primary in vitro antibody production.

Irradiation of cells. PCs were suspended in balanced salt solution to a concentration of 1×10^7 cells/ml and irradiated with 2,500 rads by using a Norelco MG150 X-ray machine (Phillips Electronics Instrument Co., N.Y.). The dose rate was 187 rads/min at 150 kV, 10 mA, and a focal distance of 40 cm.

Assay for PFC. A modification of the method of Jerne et al. (14) was employed to determine the number of PFC. The amount of diethylaminoethyl-dextran was increased to 1 mg/ml, and bottomless plates were used.

Mitogen responses. Cells were suspended in complete tissue culture medium supplemented with 5% fetal bovine serum (lot #45219, Grand Island Biological Co.) and maintained in triplicate as 0.25-ml cultures in microtiter plates (Falcon Plastics #3040) containing 5×10^5 cells/well. Replicate cultures were stimulated with various doses of concanavalin A (ConA) (twice crystallized in saturated NaCl, Miles-Yeda Ltd., Kankakee, Ill.), phytohemagglutinin (PHA) (Wellcombe Laboratories, Greenville, N.C.), and lipopolysaccharide (LPS) (Bacto-lipopolysaccharide W. S. typhosa O901, Difco Laboratories, Detroit, Mich.). DNA synthesis was measured by the addition of 1 μCi of tritiated thymidine (New England Nuclear, Boston, Mass.) at 24 h for PHA and at 48 h for ConA and LPS. Twenty-four hours after addition of tritiated thymidine, the cultures were harvested using a multiple automated sample harvestor unit (Otto Hiller Co., Madison, Wis.), and radioactivity was assayed with a Beckman liquid scintillation counter (Beckman Instruments Inc., Fullerton, Calif.). Data are expressed as mean counts per minute of triplicate cultures.

RESULTS

Effect of MLN cells from infected mice on in vitro response to SRBC of normal MLN cells. To determine whether the induction of suppressor cell activity is involved in the immunodepression associated with *T. crassiceps* infection, cells from infected mice were examined for their ability to suppress the in vitro antibody response of normal MLN cells. MLN cells from mice infected with *T. crassiceps* were mixed in varying proportions with cells from normal control mice and cocultured in vitro with SRBC (Table 1). The expected number of PFC per culture was calculated by determining the proportional contribution to PFC of the infected and normal cells added to cultures. The data do not show evidence of suppressor activity in the infected nodes. Similar results have been obtained in 15 experiments with both MLN and spleen cells.

Response of MLN cells from infected mice to mitogens. The capacity of MLN cells from normal or infected mice to respond to T-lymphocyte mitogens (ConA and PHA) and a B-lymphocyte mitogen (LPS) was examined. Pools of MLN cells were prepared from control or infected mice. Cells were cultured in triplicate, and replicate cultures were stimulated with various doses of ConA, PHA, and LPS (Table 2). There was no significant depression of the response to any of the mitogens tested. Thus, by these criteria, the T and B lymphocytes from the MLN of infected mice appear to be normal.

Function of adherent and nonadherent MLN cells from infected and normal mice in the in vitro response to SRBC. Both adherent (accessory cell rich) and nonadherent (lymphocyte rich) cells are required for an in vitro response to SRBC (21). Adherent MLN cells from control and infected mice were compared for their ability to restore the in vitro response to SRBC of normal nonadherent MLN cells (Table 3). As expected, normal adherent cells restored the response of normal nonadherent cells to control levels. In contrast, adherent cells from infected mice did not restore the re-

TABLE 1. *Effect of MLN cells from infected mice on the in vitro response of normal MLN cells to SRBC*[a]

MLN cells added to cultures:		PFC/culture			
		Expt 1		Expt 2	
Normal	Infected	Observed	Expected	Observed	Expected
6×10^6		1,644		4,453	
	6×10^6	242		271	
4.8×10^6	1.2×10^6	1,365	1,364	3,600	3,617
3×10^6	3×10^6	701	943	3,020	2,362
1.2×10^6	4.8×10^6	510	522	1,527	1,107

[a] BDF_1 mice were infected 5 to 6 weeks earlier with *T. crassiceps*. Cultures contained 6×10^6 MLN cells in 1 ml and were assayed for PFC on day 5.

TABLE 2. *Response of MLN cells from T. crassiceps-infected mice to mitogens PHA, ConA, and LPS*[a]

Mitogen	Dose (μg)	cpm[b]	
		Normal	Infected
Medium		6,138 ± 2,904	7,638 ± 1,267
PHA	0.2	26,048 ± 538	26,272 ± 1,111
	2	26,384 ± 1,265	37,569 ± 605
	4	29,256 ± 4,804	39,605 ± 2,032
ConA	0.4	321 ± 32	72 ± 17
	4	752 ± 174	216 ± 25
	8	161,529 ± 2,681	113,893 ± 8,397
LPS	1	65,451 ± 2,698	68,327 ± 3,579
	10	91,233 ± 3,530	94,359 ± 9,623
	50	92,245 ± 3,098	90,916 ± 2,099

[a] Cultures contained 5×10^5 MLN cells and represent pools of MLN cells from groups of three BDF_1 mice injected 7 weeks earlier with either *T. crassiceps* or saline.

[b] Mean from triplicate cultures ± standard error of the mean.

TABLE 3. *Ability of adherent MLN cells from normal and infected mice to restore in vitro response of nonadherent MLN cells to SRBC*[a]

MLN cells			PFC[d]
Unfractionated	Nonadherent[b]	Adherent[c]	
Normal			3,756
Infected			598
	Normal	Normal	2,585
	Normal	Infected	869
	Infected	Normal	1,870
	Infected	Infected	452

[a] Cultures contained 3×10^6 MLN cells in 0.4 ml and were assayed for PFC on day 5.

[b] MLN cells with plastic-adherent cells removed: 3×10^6 equivalent.

[c] Plastic-adherent MLN cells from 3×10^6 cells.

[d] PFC per 10^6 recovered cells.

sponse of normal nonadherent cells. These results indicate a functional defect in the adherent accessory cells of the MLN of infected mice.

Nonadherent cells from normal and infected mice were then compared for their ability to generate in vitro immune responses to SRBC with adherent cells from normal mice (Table 3). The response of nonadherent cells from infected mice was similar to the reconstituted control response in the presence of normal nonadherent cells. These results indicate that T and B lymphocytes capable of responding to antigen are present in the nonadherent cell population of MLN cells from infected mice.

Restoration of response of MLN cells from infected mice by activated PCs. The ability of PCs (a source rich in accessory cells) to restore the in vitro response to SRBC of MLN cells from infected mice was examined. Preliminary experiments with unstimulated PCs gave variable results. We therefore studied the restorative capacity of activated PCs.

Normal PCs were activated in vitro by culturing in complete tissue culture medium supplemented with 20% BacCM. After 24 h, 3×10^6 freshly isolated MLN cells from infected or control mice were added to the cultures containing BacCM-activated PCs, and the cultures were immunized with SRBC (Table 4). PCs activated by BacCM restored the response of MLN cells from infected mice to control levels. BacCM alone had little effect on the response of MLN cells from infected mice. Thus activated PCs from normal mice are capable of reconstituting a defect present in the MLN population of infected mice.

Identification of the restoring cell type in activated PCs. PCs are a heterogeneous population containing lymphocytes, accessory cells, and other cell types. To identify the restoring cell type in populations of activated PCs, the cells were depleted of functional T or B lymphocytes before being tested for their ability to restore the in vitro response of MLN cells from infected mice. PCs from normal mice were depleted of T lymphocytes by treatment with specific antiserum and complement or depleted of functional B lymphocytes by irradiation with 2,500 rads before activation in vitro with BacCM (Tables 5 and 6). PCs depleted of functional T

TABLE 4. *Restoration of in vitro response to SRBC of MLN cells from infected mice with activated PCs*[a]

Addition to culture	PFC/culture					
	Expt 1		Expt 2		Expt 3	
	Normal	Infected	Normal	Infected	Normal	Infected
Medium only	2,176	76	3,887	577	27,507	3,060
BacCM	1,632	33	5,287	1,161	21,913	2,147
1.2×10^5 PCs	10,280	2,496	5,560	4,460	28,613	21,113
6×10^4 PCs	6,853	1,164	4,747	6,180	29,493	14,100

[a] Normal PCs were activated in vitro for 24 h with BacCM before addition of MLN cells from control or infected mice.

TABLE 5. *Restoration of in vitro response to SRBC with activated PCs depleted of T cells*[a]

Addition to culture	PFC/culture	
	Normal MLN	Infected MLN
Medium only	6,850	400
BacCM	8,350	483
1×10^5 PCs	11,490	6,667
1×10^5 RAMB & C PCs[b]	8,580	6,813
1×10^5 C PCs[c]	10,700	7,080

[a] Normal PCs were activated in vitro for 24 h with BacCM before addition of MLN cells from control or infected mice.

[b] Normal PCs were depleted of T lymphocytes by treatment with rabbit anti-mouse brain serum (RAMB) and complement (C) and then activated in vitro.

[c] Normal PCs treated with complement (C) alone before activation in vitro.

TABLE 6. *Restoration of in vitro response to SRBC with irradiated activated PCs*[a]

Addition to culture	PFC/culture	
	Normal MLN	Infected MLN
Medium only	7,567	596
BacCM	7,393	688
1×10^5 PCs	8,360	4,713
1×10^5 irradiated PCs[b]	10,093	4,847

[a] Normal PCs were activated in vitro for 24 h with BacCM before addition of MLN cells from control or infected mice.

[b] Normal PCs were irradiated with 2,500 rads and then activated in vitro.

or B lymphocytes were still capable of restoring the responsiveness of MLN cells from infected mice. These results indicate that the active cell in restoring the immune responsiveness of MLN cells from infected mice is a radioresistant accessory cell. These data support the hypothesis that the immunodepression in the MLN of *T. crassiceps*-infected mice is largely due to functional defects in their accessory cell populations.

DISCUSSION

Our results provide strong evidence that the immunodepression in *T. crassiceps* infection is the result of a defect in the accessory cells of infected mice and not the result of excessive suppressor cell activity. The primary in vitro response to SRBC of MLN cells from infected mice is consistently and dramatically depressed and can be restored to control levels by addition of activated PCs from normal mice (Table 4). Activated PCs which have been depleted of functional T or B lymphocytes retain their restorative ability, indicating that the restoring cell type is a radioresistant accessory cell (Tables 5 and 6). Our failure to obtain complete restoration with unstimulated PCs is consistent with the results of others (20, 27), who found that prior stimulation in vivo or in vitro is required to obtain functional restoration with PC populations. The presence of an accessory cell defect in infected mice is further indicated by the failure of adherent MLN cells from infected mice to reconstitute the response of normal nonadherent MLN cells to control levels (Table 3).

The T and B lymphocytes of *T. crassiceps*-infected mice appear to be normal by the criterion of mitogen responsiveness (Table 2). Moreover, nonadherent MLN cells from infected mice are fully capable of generating a normal humoral immune response to SRBC with normal adherent cells (Table 3). In addition, the in vitro response to SRBC of MLN cells from infected mice can be restored by addition of accessory cell-restoring factors (R. I. Mishell and K. L. Miller, unpublished data). These data do not completely rule out alterations in T-helper function, since it is possible that reduced levels of T help in the MLN of infected mice may be offset by the added accessory cell activity (12, 25). However, the failure of adherent MLN cells from infected mice to reconstitute the in vitro response of normal nonadherent cells suggests that an accessory cell defect is the predominant lesion in *T. crassiceps*-infected mice.

Suppressor cells have been demonstrated in

infection with the nematode *Trichinella spiralis* (15), and in schistosomiasis (2, 3) and trypanosomiasis (5, 13, 24), and are thought to play an important role in the immunodepression associated with these infections. Our results indicate that induction of excessive suppressor cell activity is not a major mechanism in the immunodepression observed in *T. crassiceps*-infected mice. In 15 experiments there was no evidence for the presence of suppressor cells in either the MLN or the spleens of infected mice; typical data are shown in Table 1. Our findings agree with those of Mitchell and Handman (18) who studied the effects of infection of mice with the larval cestode *Mesocestoides corti* on the immune response to SRBC and 2,4-dinitrophenyl-Ficoll. They found no evidence that suppressor cells are involved in the immunodepression associated with *M. corti* infection. The lack of detectable suppressor cell activity in *T. crassiceps* and *M. corti* infections indicates that the induction of excessive suppressor cell activity does not always play a major role in parasite-induced immunodepression.

The defect in accessory cell activity in *T. crassiceps* infection may be due to alterations in the distribution of particular subpopulations of accessory cells or to functional alterations of the cells. Chronic inflammation of the peritoneal cavity as a result of infection may result in the migration of accessory cells to the peritoneal cavity at the expense of the lymphoid organs. Competition of the lymphoid organs with the peritoneal cavity for available accessory cells could result in immunodepression, particularly in the response of the MLN, since accessory cells are limiting in this organ (10). An accessory cell defect has been demonstrated in murine malaria (1, 11, 17, 29, 31) and is thought to be caused by functional alterations in accessory cells resulting from phagocytosis of excessive parasite debris (17). The overloading of accessory cells with parasite debris could interfere with antigen handling or factor production by accessory cells, both of which are thought to play a role in the induction and regulation of antibody synthesis (22, 30). It is also possible that parasite-derived soluble products may have modulatory effects on the activity of accessory cells either directly (32) or in the form of antigen-antibody complexes binding to the Fc receptors on the cells (9, 16). Further investigation is needed to determine the nature of the accessory cell defect in *T. crassiceps* infection. An examination of the accessory cells from infected mice for such functions as the ability to process antigen (10, 30) or to generate cooperative factors (22, 23) may help to identify the defect and the particular functions that are impaired.

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