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Concomitant Cellular and Humoral Expression of a Regulatory Cross-Reactive Idiotype in Acute *Schistosoma japonicum* Infection

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In this study the expression of a regulatory cross-reactive idiotype ($SJ\text{-}CRI_M$), which is associated with anti-soluble egg antigen (SEA) molecules in murine *Schistosoma japonicum* infection, is described. Both humoral and cellular components of the immune response were analyzed during the course of infection with *S. japonicum*. In the humoral immune response, the content of $SJ\text{-}CRI_M$ decreases as the titer of anti-SEA antibody increases throughout infection. Quantitatively, values for serum ranged from 13.8 ± 0.3 μg of $SJ\text{-}CRI_M$, which binds anti-idiotypic antibody per ml of serum at 6 weeks postinfection, to 1.3 ± 1.8 μg/ml at 30 weeks postinfection. Analysis of splenic cell subpopulations for expression of $SJ\text{-}CRI_M$ revealed that only splenic B cells expressed $SJ\text{-}CRI_M$ during acute infection (5 to 10 weeks postinfection). On the other hand, thymic cells with a high expression of the $SJ\text{-}CRI_M$ and Ly-1 marker were observed in acute infections up to 15 weeks postinfection. These data indicate that $SJ\text{-}CRI_M$-bearing T cells are selectively localized in acute infection. In addition, the disappearance of expression of $SJ\text{-}CRI_M$ in serum and cells of chronically infected animals parallels the modulation of granulomatous inflammation and portal hypertension. Results of this study suggest that expression of $SJ\text{-}CRI_M$ on anti-SEA molecules could represent a marker for acute infection, while its disappearance from serum serves as a marker for modulation of disease.

Modulation of granulomatous inflammation around schistosome eggs occurs in inbred mice as infection progresses from acute to chronic. This process results in smaller egg granulomas and lower portal pressures (1, 8, 29), as well as a decrease in immediate and delayed footpad hypersensitivity reactions to soluble egg antigens (SEA) (2, 16) after 10 to 15 weeks of infection. In *Schistosoma japonicum* infection, modulation is mediated in part by suppressive serum components (17, 29). Thus, the adoptive transfer of serum (29) or its immunoglobulin G1 (IgG1) fraction (30) from chronically infected mice reduces granulomatous inflammation and portal pressure in vivo and SEA-induced proliferative responses in vitro (17). Results of recent studies (27) have shown that both anti-SEA antibodies and anti-idiotypic antibodies mediate this process in vitro. Specifically, anti-idiotypic antibodies observed in chronic infection, which described a major cross-reactive idiotype that occurred on anti-SEA molecules ($SJ\text{-}CRI_M$), were the most potent immunosuppressive molecules. In addition, a recent study (G. R. Olds, T. Bonfield, and T. F. Kresina, submitted for publication) has shown that $SJ\text{-}CRI_M^+$, monoclonal anti-SEA antibodies are comparatively more potent immunosuppressive moledules on a per weight basis than $SJ\text{-}CRI_M^-$ anti-SEA monoclonal antibodies. Results of these studies strongly suggest that network components related to the major cross-reactive idiotype observed in *S. japonicum* infection mediate immune modulation during the chronic stages of disease. In light of these observations, this study was performed to describe in detail the expression of the major cross-reactive idiotype ($SJ\text{-}CRI_M$) in both humoral and cellular components of the immune response during the course of *S. japonicum* infection. The data suggest that the expression of $SJ\text{-}CRI_M$ by anti-SEA antibodies may represent a marker for acute infection and its disappearance serves as a marker for immunomodulation of disease.

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MATERIALS AND METHODS

Animals and infection. C57BL/6 mice (Jackson Laboratory, Bar Harbor, Maine) were infected with 25 cercariae of a Philippine strain of *S. japonicum* at Lowell University, Lowell Mass. (National Institute of Allergy and Infectious Diseases supply contract AI-02636). Animals with this intensity of infection will survive at least 30 weeks postinfection (29).

Assay for anti-SEA antibody. SEA was prepared from the livers and intestines of infected CF1 mice (Charles River Breeding Laboratories, Inc., Cambridge, Mass.), as described previously (2, 17). Anti-SEA antibody activity of serum was determined by a solid-phase enzyme-linked immunosorbent assay in a microtiter assay (27). Serum was diluted serially (neat to >1:20,000). The last dilution that was statistically higher than normal serum controls was considered the end titer.

Serological analysis of serum anti-SEA antibody. The presence of $SJ\text{-}CRI_M$ on anti-SEA antibodies was determined by an indirect method of precipitation, as described previously (27). Autologous polyclonal anti-idiotypic antibody specifically purified from chronic (30-week) infected mouse serum was used as the labeled ligand. In previous studies (27), this polyclonal anti-idiotype preparation was used to define the appearance of $SJ\text{-}CRI_M$ on anti-SEA antibodies derived from acute infections. In this study serial dilutions (1:10 to 1:320) of serum from infected animals were mixed with 100 ng of ^{125}I-labeled polyclonal anti-idiotypic antibody in the presence of 10 μg of normal C57BL/6 immunoglobulin. The mixture was incubated for 1 h at 37°C, and immune complexes were precipitated as described above. Data are presented as anti-idiotypic binding capacity of the monoclonal antibodies which was derived from the penultimate value on

TABLE 1. Presence of SJ-CRI$_M^+$ molecules in serum of individual mice during the course of *S. japonicum* infection[a]

Animal no.	wk of infection	Anti-SEA titer[b]	Anti-idiotype binding capacity (IBC/ml ± SD)[c]
1	6	1/16	15.0 ± 0.7
2	6	1/4	9.0 ± 0.3
3	6	1/32	4.7 ± 0.3
4	6	1/64	3.9 ± 0.7
5	6	1/64	11.5 ± 0.4
6	6	1/32	5.8 ± 0.6
7	12	1/16	1.1 ± 0.5
8	12	1/16	0.8 ± 0.8
9	12	1/256	5.6 ± 4.0
10	12	1/128	2.2 ± 1.4
11	12	1/128	1.7 ± 0.7
12	12	1/256	4.1 ± 2.3
13	15	1/128	0.0 ± 0.0
14	15	1/64	2.7 ± 2.7
15	15	1/512	5.8 ± 0.1
16	15	1/1,024	5.6 ± 0.3
17	15	1/128	0.1 ± 0.8
18	15	1/64	1.4 ± 1.5
19	20	1/256	3.3 ± 1.1
20	20	1/4,096	1.3 ± 0.2
21	20	1/1,024	1.6 ± 0.8
22	30	1/4,096	0.6 ± 0.8
23	30	1/8,192	0.0 ± 0.0
24	30	1/1,024	0.0 ± 0.0

[a] C57BL/6 mice were infected with 25 *S. japonicum* cercariae and individually bled during the course of infection. The presence of SJ-CRI$_M$, the major cross-reactive idiotype found during *S. japonicum* infection, was determined by using an indirect precipitation assay for the binding of ^{125}I-labeled specifically purified 30-week anti-idiotypic antibodies.

[b] Anti-SEA titer was determined after serial 1:2 dilutions of infected or control serum. The last dilution which was statistically higher than levels in normal mouse serum was considered the end titer. Data are presented as mean end titer for duplicate samples.

[c] Anti-idiotype binding capacity is derived from the penultimate value on the linear portions of the binding curve of 100 ng of ^{125}I-labeled anti-idiotypic antibodies with diluted serum samples.

the linear portion of the binding curve, as described previously (27).

Preparation of cells. Thymus cells were prepared by removing the thymus by retrosternal dissection. A single cell suspension of cells was made at 4°C with Dulbecco modified Eagle medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum (FCS) (Hyclone; Logan, Utah). These cells were >85% Thy-1.2 positive, as determined by complement lysis and trypan blue dye exclusion. Spleens were also removed, and single cell suspensions of splenocytes were prepared in cold DMEM with 10% FCS (17). Unfractionated spleen cells were used, or enriched subpopulations were prepared. T-cell-enriched populations were prepared by passage over a 600-mg acid-washed nylon wool column for 30 min at 37°C. Over 95% of the effluent cells were lysed by treatment with monoclonal anti-Thy-1.2 (Cedarlane Laboratories, Hornby, Ontario, Canada) plus compliment. Enriched B cells were prepared by treatment of splenocytes with monoclonal anti-Thy-1.2 and compliment. Splenocytes (5×10^6) were suspended in 250 μl of DMEM in a glass tube (10 by 75 mm). In this tube 250 μl of anti-Thy-1.2 monoclonal antibody diluted 1/20 with DMEM was added. Cells were incubated for 30 min at 37°C in 5% CO_2 and then washed. To each tube was added 250 μl of rabbit low-tox complement (Cedarlane) diluted 1/8 with DMEM. After an additional 10-min incubation, cells were washed repeatedly. The viability of all cell preparations was determined by trypan blue dye exclusion (average, 88 to 94%) and used at a concentration of 2×10^5 viable cells per well.

Serological analysis of lymphoid cells. Thymocytes, splenic cells, or enriched subpopulations of splenic cells were analyzed for expression of SJ-CRI$_M$ by direct binding of radiolabeled anti-idiotypic antibodies in the presence of excess normal mouse immunoglobulin. Thymic cells were additionally analyzed for expression of Thy-1.2, Ly-1.2, and Ly-2.2. In brief, 2×10^5 cells were fractionated into 96-well microtiter plates. Cells were suspended in 50 μl of DMEM supplemented with 10% FCS and penicillin-streptomycin. Labeled ligand (10^6 cpm; anti-idiotypic antibody, anti-Thy-1.2, anti-Ly-1, anti-Ly-2) and 10 μg of normal C57BL/6 mouse immunoglobulin were added in 20 μl of DMEM. Plates were incubated at 37°C with 10% CO_2 for 1 h, washed 10 times with DMEM, and harvested in a mini-mash harvester. Data are presented as picograms of labeled ligand bound per well (2×10^5 cells) above background binding of radiolabeled normal mouse IgG which ranged from 3.4 to 6.3% total counts per minute.

Reagents. Anti-idiotype antibody describing SJ-CRI$_M$, the major cross-reactive idiotype associated with anti-SEA antibodies, was specifically purified from sera of pooled chronically infected mice as described previously (27). Specifically purified monoclonal anti-Thy-1.2 was obtained from Miles Scientific (Div. Miles Laboratories, Inc., Naperville, Ill.). Specifically purified monoclonal anti-Ly-1.2 and anti-Ly-2.2 were obtained from Becton Dickinson and Co. (Mountain View, Calif.). Reagents were radiolabeled by the chloramine T method (19), and the specific activities (in counts per minute per nanogram) were as follows: anti-idiotypic antibody, 6,570; anti-Ly-1, 10,175; anti-Ly-2, 4,781; anti-Thy-1.2, 3,559; mouse immunoglobulin (DEAE purified), 11,248. Data are expressed as weight of labeled ligand bound due to the various specific activities of the reagents.

RESULTS

Presence of SJ-CRI$_M$ on serum anti-SEA molecules. Individual serum samples, as well as pooled serum samples from

TABLE 2. Presence of SJ-CRI$_M^+$ molecules in pooled serum samples from 25 mice during the course of *S. japonicum* infection[a]

Sample no.	wk of infection	Anti-SEA titer[b]	Anti-idiotype binding capacity (IBC/ml ± SD)[c]
1	Control[d]	0	0.0 ± 0.0
2	6	1/4	13.8 ± 0.3
3	10	1/16	4.8 ± 1.3
4	12	1/64	1.6 ± 2.2
5	15	1/256	4.0 ± 2.4
6	20	1/1,024	3.0 ± 0.2
7	25	1/4,096	1.9 ± 2.7
8	30	1/4,096	1.3 ± 1.8

[a] Sera from 25 to 50 *S. japonicum*-infected (25 cercariae) mice were pooled at various times after infection (week of infection). The presence of SJ-CRI$_M$ was determined by the binding of ^{125}I-labeled 30 anti-id antibody which describes SJ-CRI$_M$.

[b] Anti-SEA titer was determined by end titer ELISA.

[c] Anti-idiotype binding capacity was determined by indirect precipitation of formed immune complexes comprising ^{125}I anti-id antibody with serial dilutions of serum samples.

[d] Uninfected.

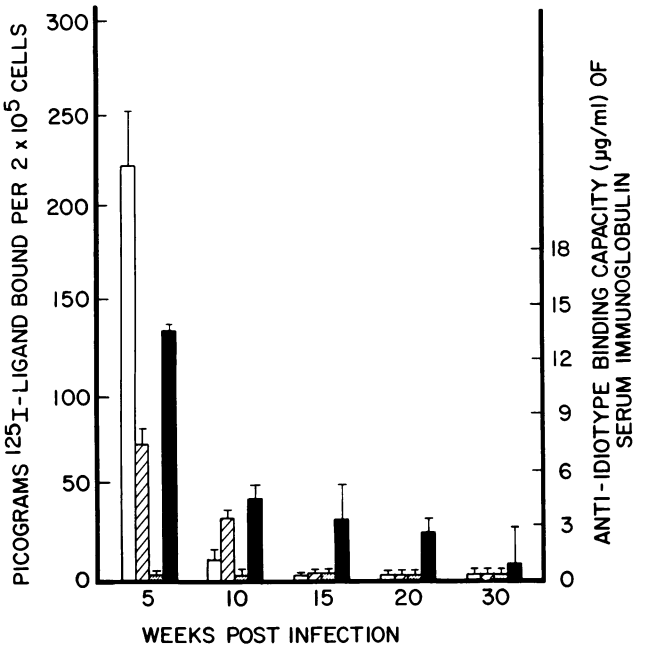

FIG. 1. Expression of SJ-CRI$_M$ by unfractionated splenic cells (□), splenic B cells (▨), splenic T cells (▨), and anti-SEA antibody in serum (■) during the course of *S. japonicum* infection. Detection of SJ-CRI$_M$ in cellular populations was performed by direct binding with ^{125}I-labeled anti-idiotypic antibody. Data are presented as picograms of labeled ligand bound minus that of control (^{125}I-labeled normal C57BL/6 IgG) values. For immunoglobulin in serum, data are presented as the binding capacity of anti-SEA antibody in serum to ^{125}I-labeled anti-idiotypic antibody. Presented in this fashion, anti-idiotype binding capacity is a measure of SJ-CRI$_M$ and not total anti-SEA activity.

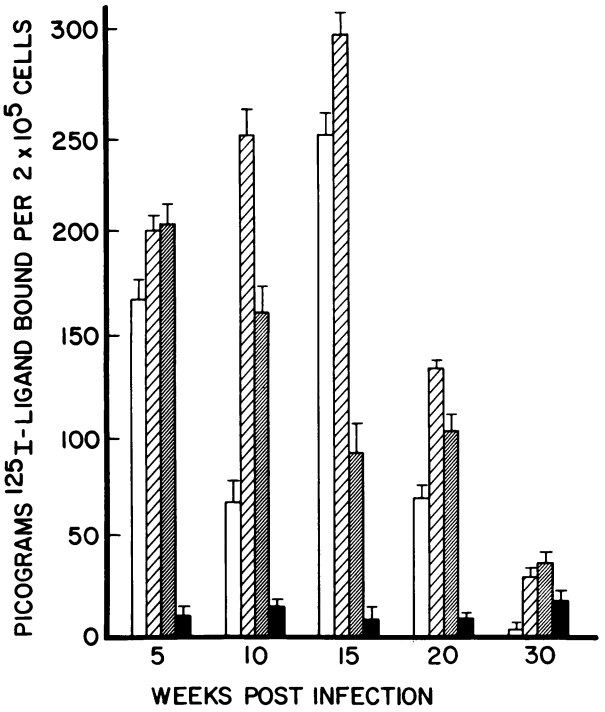

FIG. 2. Profile of the cell surface phenotype of thymocytes from infected mice during the course of *S. japonicum* infection. Assay of the cell surface phenotype of cells was by a direct binding assay with ^{125}I-labeled anti-idiotypic antibody (□), anti-Thy-1.2 antibody (▨), anti-Ly-1 antibody (▨), and anti-Ly-2 antibody (■). Data are presented as picograms of labeled ligand bound minus that of control (^{125}I normal C57BL/6 IgG) values.

various time points during the course of infection, were assayed for anti-SEA activity and binding to polyclonal anti-idiotype antibody which describes SJ-CRI$_M$. The data for individual serum samples are presented in Table 1. Sera from six C57BL/6 mice were assayed at 6, 12, and 15 weeks postinfection. The sera from these animals showed increasing anti-SEA activity but decreasing anti-idiotype binding capacity ($P < 0.05$). For these samples, the average anti-idiotype binding capacity of anti-SEA antibodies decreased from 8.3 ± 4.0 μg/ml at 6 weeks to 2.6 ± 2.4 μg/ml at 15 weeks postinfection (mean values of six sera). Analysis of individual serum samples from animals with chronic infection (20 to 30 weeks) revealed low levels of expression of SJ-CRI$_M$ (Table 1). These studies correlate well with the data presented in Table 2, in which is described the expression of SJ-CRI$_M$ in pooled serum samples from groups of infected animals. For both individual and pooled serum samples, as the titer of anti-SEA antibody increased with time of infection, the presence of SJ-CRI$_M$ (the ability to bind polyclonal anti-idiotype antibodies) on polyclonal anti-SEA decreased. SJ-CRI$_M$ reactivity, in fact, was virtually absent during chronic infection. However, among individual animals at any given time point no inverse correlation could be demonstrated.

Expression of SJ-CRI$_M$ on splenic cells of infected animals. Splenic cells and subpopulations of splenic cells were analyzed for the expression of SJ-CRI$_M$ during the course of infection. Splenic cells could be shown to bind ^{125}I-labeled anti-idiotypic antibody in the presence of excess normal mouse immunoglobulin at 5 weeks postinfection (Fig. 1). Analysis of the subpopulations of splenic cells revealed that enriched fractions of B cells isolated from animals acutely infected with *S. japonicum* (5 to 10 weeks) expressed SJ-CRI$_M$. Splenic cell fractions enriched for T cells were not observed to bind SJ-CRI$_M$ above control values throughout infection. These data, coupled with the observed serum expression of SJ-CRI$_M$, indicate that during acute infection, SJ-CRI$_M$ is observed in serum as well as in splenic B cells which express surface SJ-CRI$_M$.

The expression prolife of SJ-CRI$_M$, Thy-1, Ly-1, and Ly-2 on thymic cells during the course of infection is shown in Fig. 2. In contrast to splenic T cells, thymic cells bind anti-idiotypic antibodies to a high degree during acute infection (5 to 15 weeks postinfection). These cells also express Thy-1 and Ly-1 surface markers in large quantities. The marker Ly-2 is only marginally expressed in thymic cells from acutely infected mice. These data indicate that during acute infection, a population of cells can be found in the thymus of infected mice with the surface phenotype Thy-1$^+$ Ly-1$^+$2$^-$ SJ-CRI$_M^+$. By noting this cell surface phenotype, it can be postulated that this cellular population could be a source of idiotype-specific T helper cells utilized in the expression of SJ-CRI$_M^+$ in serum. Studies are in progress to address this question.

DISCUSSION

The prominent pathologic lesion in schistosomiasis is the granulomatous inflammation that occurs around parasite eggs trapped in the host tissues (25). In *S. japonica* infection

this occurs in the presinosoidal spaces of the liver. As disease progresses from acute to chronic, a beneficial immunologic down regulation, termed modulation, occurs which results in smaller hepatic egg granulomas (29) and diminished in vitro responses to soluble SEAs (16). Granuloma formation around parasite eggs appears to be a delayed hypersensitivity response to SEA and is primarily a T-cell-dependent event (4, 28). Modulation in murine *S. japonicum*, however, appears to be dependent not only on intact T cells but also intact B cells in the infected host (3). The adoptive transfer of either serum from chronically infected mice (20 to 30 weeks) or T cells from animals infected for 10 to 15 weeks (35) into acutely infected recipient mice modulates granulomatous inflammation and portal pressure in vivo. Cheever et al. (4) have supported this dual concept of regulation by showing that nude mice form smaller egg granulomas from the beginning of egg deposition in vivo, while B-cell-deficient mice (anti-IgM treated) have larger granulomas at 15 weeks of infection but not at 7 weeks when compared with untreated control mice (3). Results of these studies indicate that both T- and B-cell circuits are involved in the formation and subsequent modulation of egg granulomas. Serum and T cells from chronically infected mice reduce granulomatous inflammation and portal pressure in vivo (30) and also inhibit SEA-induced blastogenic responses or immunoglobulin synthesis in vitro (17, 34). While these regulatory T cells appear to be of the Lyt-2^+ phenotype, the serum components have been shown to be naturally occuring IgG1 polyclonal idiotypic antibodies and naturally occurring IgG1 polyclonal anti-idiotypic antibodies directed toward unique epitopes on anti-SEA molecules (27). Two populations of serologically distinct naturally occurring anti-idiotypic antibody populations appear sequentially during infection with *S. japonicum*. Early in the course of infection anti-idiotypic antibodies are observed that describe a minor cross-reactive idiotypic population of anti-SEA antibodies. These anti-idiotypic molecules (from acute infection) do not suppress SEA-induced proliferative responses and therefore appear not to be regulatory molecules. A second population of anti-idiotypic antibodies, which describes a major cross-reactive idiotypic population of anti-SEA molecules, appears during chronic infection. These latter anti-idiotypic antibodies are antigen-combining, site-specific, and highly suppressive in lymphoproliferation assays. These observations suggest that immune network components mediate immune modulation in chronic *S. japonicum* infection. Idiotypic control of immune responses was first suggested by Jerne (22) and now appear to be important in the host response to several well-defined antigens (14, 20) and in response to several infectious agents (11, 26, 33, 34). The occurrence of autologous immune network components regulating granulomatous inflammation has not been shown previously for parasitic diseases. Certain immune network components, however, have been examined recently in another schistosome species. Powell and Colley (32) have found auto anti-idiotypic antibodies directed toward anti-SEA antibodies in mice infected with *Schistosoma mansoni*. The role of these antibodies in immune modulation in that species is still unknown. Grzych et al. (18) have artificially manipulated the network to produce protective immune responses in rats. Using a rat monoclonal anti-idiotypic antibody directed toward the antigen (38,000-molecular-weight glycoprotein) combining site of a protective rat monoclonal IgG2a antibody, they were able to protect rats from a challenge with *S. mansoni* cercariae. Results of these studies support the evidence that network immune interactions, that is, idiotypic and anti-idiotypic interactions, mediate immune modulation in murine *S. japonicum*. The exact connection between B-cell products, T suppressor cells, and their presumed target, a Lyt-1^+ helper T cell, are unknown but could involve the induction of anti-idiotype bearing suppressor T cells.

In this study the expression of SJ-CRI_M in serum and on B cells was found predominantly during acute infection, with SJ-CRI_M expression being exhibited longer in serum than on splenic B cells. This observation of prolonged expression of SJ-CRI_M in serum likely reflects both clonal deletion of SJ-CRI_M-bearing B cells in acute infection and the relatively long half-life of immunoglobulin molecules in serum. The presence of SJ-CRI_M-bearing T cells in thymic cells but not in splenic T-cell subpopulations of acutely infected mice suggests that these cells are selectively localized. In this regard, a recent study, in which the expression of a cross-reactive idiotype on rheumatoid factor was described in patients with Sjogren's syndrome (15), noted a selective localization of CRI-bearing B cells in the salivary gland of patients with non-Hodgkins lymphoma. Patients with Sjogren's syndrome without sicca symptoms did not contain B cells that expressed CRI. In addition, surface immunoglobulin idiotype has also been utilized as a detection marker for various B-cell lymphomas (23, 24, 31).

SJ-$CRI_M{}^+$ expression on cells in the thymus was found predominately at two times (5 and 15 weeks postinfection). These cells were found at a time of augmented Thy-1.2 expression, which is indicative of maturational changes. It is intriguing to speculate that the earlier time points of augmented SJ-$CRI_M{}^+$ expression represents Thy-1^+ Ly-1^+2^- SJ-$CRI_M{}^+$ helper lymphocytes destined to participate in hepatic granulomas. The second population of SJ-$CRI_M{}^+$ cells could reflect Ly-1^+2^- suppressor inducer cells, so-called T_{s1} cells (10, 12, 13), which would initiate the onset of immune modulation observed in chronic infection (27). These cell types have precedence in the augmentation and modulation of immune responses in murine schistosomiasis (5, 6, 35).

Finally, the data from this study demonstrate a serologic cross-reactivity between T and B cells as well as immunoglobulin in serum. This is particularly relevant because both components of the immune response appear to be involved in immune modulation of this disease (30). Such an observation has been made in immune responses to other antigens but does not imply structural identity. Numerous data challenge the concept that T and B cells carry identical V_H regimens (9, 21). These data, however, do not preclude serologic relatedness. Auto-anti-idiotypic immunoglobulin has been found to inhibit T-cell-mediated responses not only in *S. japonicum* infection (27) but following infection of mice with the *Mycobacterium bovis* BCG (7). In this study, however, no direct correlation between these serologic changes and modulation in vivo was attempted.

In summary, in this study is described the expression of an autologous component of the immune network which has been shown to have immunoregulatory capacity (27). The expression of SJ-CRI_M, the major cross-reactive idiotype associated with anti-SEA antibodies in *S. japonicum* infection, was shown to predominate during acute infection. The observation that SJ-$CRI_M{}^+$ molecules are preferentially expressed in acute infection suggests that SJ-CRI_M may represent a marker for the acute stages of disease. In addition, the lack of expression in chronic infection, at a time of increasing anti-SEA antibody titers, indicates that the disappearance of SJ-CRI_M may represent a marker for modulation of disease and may be modulated by anti-SJ-CRI_M.

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