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Soluble Intercellular Adhesion Molecules in Human Schistosomiasis: Correlations with Disease Severity and Decreased Responsiveness to Egg Antigens

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Granuloma formation, the principal pathologic consequence of infection with *Schistosoma mansoni*, is a complex process involving intricate cell-cell interactions in which intercellular adhesion molecules are likely to participate. To examine this possibility, sera of schistosomiasis patients in various clinical groups were assayed for the presence of soluble intercellular adhesion molecule 1 (sICAM-1) and soluble E-selectin (sE-selectin). Comparisons were made between groups with different infection intensities (as predicted by fecal egg count) as well as between groups with severe (hepatosplenic) or milder (intestinal) pathology. All groups had elevated levels of sICAM-1 compared with controls. Also, patients in the high egg-excreting and hepatosplenic groups had significantly higher levels of serum sICAM-1 than patients in the low-egg-excreting and intestinal groups, respectively. The levels of sE-selectin were significantly elevated in the sera of all patients except those in the hepatosplenic group compared with controls. Patients in the intestinal group had significantly higher levels of sE-selectin in their sera than did hepatosplenic group patients, but serum sE-selectin levels of high- and low-egg-excreting patients were comparable. A striking finding of this study was the inverse correlation observed between sICAM-1 levels and peripheral blood mononuclear cell responses to schistosome soluble egg antigens (SEA) but not with responses to other schistosome antigens, purified protein derivative, or mitogen. Because ICAM-1 can perform a costimulatory function in antigen-presenting cell–T cell interactions, it is possible that shedding of ICAM-1 in the granuloma microenvironment interrupts proper costimulation, leading to unresponsive SEA-specific T cells. In this way, sICAM-1 could be one factor contributing to the observed modulation of cellular responses to SEA in chronic human schistosomiasis.

The pathology associated with *Schistosoma mansoni* infections results from parasite eggs lodging in the presinusoidal capillaries of the liver where they stimulate granuloma formation. Granulomas are highly organized cellular lesions orchestrated by T cells responding to egg antigens (19, 34, 38). Although T cells control this event, several cell types interacting with each other as well as with the extracellular matrix are important for overall granuloma architecture. Integrins, selectins, and cytokines are important for cell-cell communication among both hematopoietic and nonhematopoietic cell types and thereby provide a variety of mechanisms by which these cells can influence one another (48, 49). The effect of cytokines in schistosomal infections continues to be an area of intense research; however, investigation of the role of cellular adhesion molecules in this disease has begun only recently (42).

One of these adhesion molecules, intercellular adhesion molecule 1 (ICAM-1; CD54), is a cell surface glycoprotein belonging to the immunoglobulin superfamily of proteins (48–50). It is present on endothelial cells, antigen-presenting cells, and fibroblasts (16, 48, 49). Typically, it is expressed at low levels on these cells, but increased expression can be induced by interleukin-1, gamma interferon (IFN-γ), or tumor necrosis factor alpha (TNF-α) (16, 17, 49). ICAM-1 performs several vital roles in the normal functioning of the immune system. For example, lymphocytes and other leukocytes interact with ICAM-1 on vascular endothelial cells during recruitment into tissues undergoing inflammatory responses (9, 10, 17, 21, 29, 48, 52). Also, T-cell interactions with ICAM-1 on antigen-presenting cells stabilize the cell-cell interaction and reduce the threshold for antigen-specific activation (15, 20, 28, 35, 44, 55). Thus, ICAM-1 performs an important function in directing cells to sites of inflammation as well as activating them once they arrive.

Another important participant in diapedesis is endothelial leukocyte adhesion molecule 1 (E-selectin; ELAM-1). This molecule is a member of the selectin family of intercellular adhesion molecules and participates in the initial attachment of leukocytes to vascular endothelium during cellular emigration (5, 30, 48). E-selectin is not expressed on resting endothelial cells but, like ICAM-1, can be induced by interleukin-1, TNF-α, or lipopolysaccharide (6, 7, 30). E-selectin is described primarily as a receptor for neutrophil transendothelial migration, but it can also serve as a receptor for eosinophils (29, 56), monocytes (11, 25), natural killer cells (31), and $CD4^+$ memory T cells (24, 31, 39, 47). The tissue location of and specific cytokine stimulus to the vascular endothelium determine which leukocyte population(s) adheres (37, 46).

Recently, soluble forms of ICAM-1 and E-selectin have been described. The structure of soluble ICAM-1 (sICAM-1) is consistent with a membrane-cleaved variant of cellular ICAM-1 and maintains its ligand-binding ability (40, 43). The physiologic function of sICAM-1 is unknown, but interestingly, its release from cells is effected by some of the same cytokines which cause upregulation of cell surface expression (2, 40). Elevated levels of sICAM-1 are noted in several disease

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TABLE 1. Composition of clinical groups

Clinical group	Age (yr)		Sex (no. of males/no. of females)	Inclusion criteria
	Mean ± SD	Range		
Low egg excreting	13.1 ± 3.4	5–22	15/24	Geometric mean EPG of ≤400
High egg excreting	12.9 ± 3.3	5–23	13/26	Geometric mean EPG of ≥800
Intestinal	34.0 ± 10.5	15–55	26/15	Egg positive; no organomegaly
Hepatosplenic	34.1 ± 10.5	15–56	26/15	Firm, palpable liver and spleen

conditions (reviewed in reference 23). Like sICAM-1, soluble E-selectin (sE-selectin) is a truncated version of the cell surface form and maintains the ability to bind its ligand (30, 31, 40). Therefore, soluble adhesion molecules, like their membrane-bound counterparts, may affect cell-cell interactions.

Because the highly organized structure of periovular granulomas in schistosomiasis requires complex cell-cell interactions, adhesion molecules are potentially important in granuloma formation. This idea is supported by the recent work of Ritter et al. demonstrating ICAM-1 expression in association with early granuloma formation in schistosome-infected mice (42). In addition, some cytokines which are involved in granuloma formation (e.g., interleukin-1, TNF-α, and IFN-γ) (1, 13, 14, 26) are also associated with increased levels of cell surface and soluble adhesion molecules (2, 6, 7, 16, 17, 30, 40, 49). To begin the evaluation of the role of adhesion molecules in human schistosomiasis, the sera of patients with *S. mansoni* infections were studied to determine if sICAM-1 and sE-selectin levels were altered as a result of disease status. Correlations between soluble adhesion molecule levels and immunologic responsiveness were also examined.

MATERIALS AND METHODS

Patient groups. The individuals examined in this study were primarily residents of the rural villages of Itaquara and Itiriçu in the state of Bahia, Brazil. Diagnosis of infection and estimation of fecal egg count were performed by using the modified Kato-Katz method. Three stool samples from each patient were collected on consecutive days, and a geometric mean number of eggs per gram of stool (EPG) was calculated for each individual. As is common in field populations, many of the patients were also infected with *Ascaris lumbricoides* and/or *Trichuris trichiura*. The presence of infections other than schistosomiasis was recorded for comparison during data analysis. Hookworm infections were absent in these patients. Hepatosplenic patients were residents of various villages in Bahia who had enlarged, fibrotic livers and spleens and had been admitted to the Roberto Santos Hospital in Salvador, Bahia, for splenectomy and portal shunt surgery. The numbers of high-egg-excreting patients (EPG > 800) and patients with severe (EPG > 800) pathology (hepatosplenic patients) were much smaller than the numbers of low-egg-excreting (EPG < 400) patients and patients with milder pathology (intestinal patients) in the overall population. As a result, patient selection for testing was based on those individuals from the low-egg-excreting and intestinal groups which most closely matched the age and sex of individuals in the more limited high-egg-excreting and hepatosplenic groups. The makeup of the various patient groups is presented in Table 1. Normal controls were members of the laboratory who had never lived in areas where schistosomiasis is endemic. Informed consent was obtained from patients prior to collection of blood. All patients were subsequently treated for schistosomiasis and other parasitic infections.

Determination of sICAM-1, sE-selectin, and TNF-α. Blood for serum component analyses was collected into glass tubes and allowed to coagulate overnight at 4°C. Serum levels of sICAM-1, sE-selectin, and TNF-α were estimated by a two-site enzyme-linked immunosorbent assay (ELISA). The sICAM-1 and sE-selectin ELISAs (Bender MedSystems, Vienna, Austria) and the TNF-α ELISA (Innogenetics, Antwerp, Belgium) were purchased from Biosource International (Camarillo, Calif.). Assays were performed as described in the manufacturer's specifications, and A_{450}s were read on a UVmax Microplate Reader (Molecular Devices, Menlo Park, Calif.). Standard curves were constructed and sample concentrations were determined by using the Softmax software package (Molecular Devices).

Proliferation assays. Blood for cellular proliferation studies was collected in the presence of heparin (20 U/ml), diluted 1:2 with RPMI 1640 (Gibco BRL, Grand Island, N.Y.), layered onto Ficoll-Hypaque (Pharmacia, Piscataway, N.J.), and centrifuged at 400 × *g* for 40 min at room temperature. Peripheral blood mononuclear cells (PBMCs) were harvested and washed three times in RPMI 1640, counted on a hemocytometer, and plated in 96-well plates (no. 3596; Costar, Cambridge, Mass.) at 2.5×10^5 cells per well in RPMI 1640 containing 5% normal human serum, 3% penicillin-streptomycin, and 1% L-glutamine (all obtained from Gibco). Cells were stimulated with soluble egg antigen (SEA), soluble worm antigenic preparation, cercarial antigenic preparation, schistosome triose phosphate isomerase, or *Mycobacterium tuberculosis* purified protein derivative at a final concentration of 5 μg/ml. Mitogen (phytohemagglutinin) stimulation was at a final concentration of 2.5 μg/ml. Cultures were maintained at 37°C in a CO_2-enriched environment for 5 days. Tritiated thymidine (0.5 μCi per well, 5 Ci/mmol; Amersham, Arlington Heights, Ill.) was added for the final 8 h of culture. Cells were harvested onto glass fiber filters and processed for scintillation counting, and incorporation of tritiated thymidine was recorded as counts per minute (cpm). Data were expressed as experimental cpm divided by control cpm (E/C) as well as experimental cpm minus control cpm (E − C).

Statistical analyses. To compare levels of soluble adhesion molecules in different clinical groups, the Kruskal-Wallis nonparametric analysis-of-variance test was used. The more stringent nonparametric analysis was used because the standard deviations between some groups were of different sizes, making the standard analysis-of-variance test inappropriate. Correlations among levels of soluble adhesion molecules and proliferative responses were analyzed by simple regression analysis as well as Spearman rank correlation. Simple regression analysis was used to determine the sample correlation coefficient (*r*) and to perform residual analysis. The Spearman rank correlation was used for nonparametric regression analysis of the data.

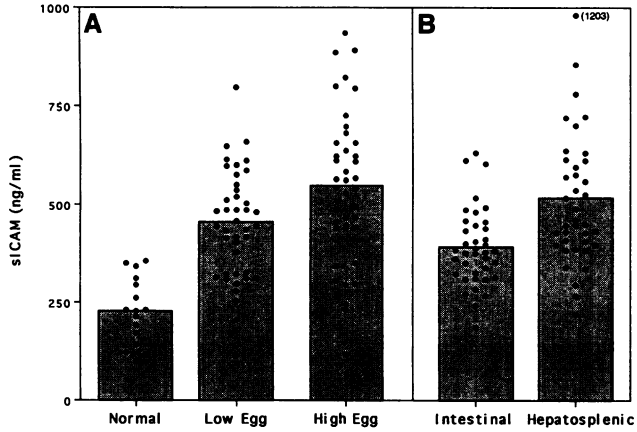

FIG. 1. Levels of serum sICAM-1 in schistosomiasis patients. A two-site ELISA was used to measure sICAM-1 levels in schistosomiasis patients who were excreting low (<400 EPG) or high (>800 EPG) numbers of schistosome eggs in their feces (A) or had the intestinal or hepatosplenic form of disease (B). Each point represents one patient; bars represent group means. Statistical analysis was performed by nonparametric analysis of variance (Kruskal-Wallis test). Serum sICAM-1 levels in all groups were significantly different ($P < 0.001$ for each) from that of the normal control group. The serum level of sICAM-1 was also significantly different between low- and high-egg-excreting groups ($P < 0.05$) and between intestinal and hepatosplenic groups ($P < 0.005$).

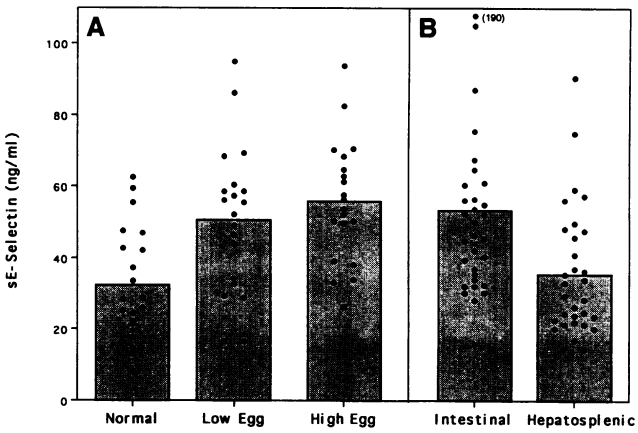

FIG. 2. sE-selectin levels in sera of schistosomiasis patients. Sera from groups of patients who were high- or low-egg-excreting (A) or had intestinal or hepatosplenic disease forms (B) were tested for levels of sE-selectin by a two-site ELISA. High- ($P < 0.001$) and low- ($P = 0.02$) egg-excreting and intestinal ($P = 0.005$) groups had significantly different serum sE-selectin levels than the never-infected controls. Intestinal group patients had significantly higher levels of sE-selectin in their sera than did hepatosplenic group patients ($P = 0.005$).

RESULTS

Soluble ICAM-1 levels are elevated in schistosomiasis patients. The aim of this study was to evaluate the levels of soluble adhesion molecules in age- and sex-matched individuals with differences in disease intensity or pathology. In the study population, individuals with high egg excretion (which is associated with greater intensity of infection and disease susceptibility [4]) were mostly young adolescents, while severe hepatosplenic disease typically manifests itself in older individuals with more established disease. Therefore, to compare these more severe forms with appropriate age- and sex-matched controls, it was necessary to create four patient groups (Table 1). Sera from high- and low-egg-excreting individuals (Fig. 1A) and from hepatosplenic and intestinal patients (Fig. 1B) were measured for sICAM-1 levels. All patient groups had significantly elevated levels of sICAM-1 when compared with individuals who had never been infected with the disease ($P < 0.001$; mean ± standard error of the mean of controls = 227.5 ± 25.2 ng/ml). In addition, high-egg-excreting individuals had significantly higher levels of sICAM-1 than low-egg-excreting individuals (544.7 ± 29.8 ng/ml versus 454.4 ± 20.3 ng/ml; $P < 0.05$), and hepatosplenic patients had significantly higher levels of sICAM-1 than intestinal patients (513.9 ± 29.4 ng/ml versus 389.7 ± 15.8 ng/ml; $P < 0.005$). Thus, higher levels of sICAM-1 were present in the sera of patients with more-severe disease states. There were no correlations observed between sICAM-1 levels and infection with *A. lumbricoides* or *T. trichiura* (data not shown).

sE-selectin levels in schistosomiasis patients. As with sICAM-1, sE-selectin levels were tested in the sera of patients with various clinical forms of schistosomiasis (Fig. 2). There were significant differences between never-infected controls (mean ± standard error of the mean = 32.1 ± 3.3 ng/ml) and high-egg-excreting (55.7 ± 4.6 ng/ml; $P < 0.001$), low-egg-excreting (50.7 ± 4.9 ng/ml; $P = 0.02$), and intestinal (53.2 ± 5.5 ng/ml; $P = 0.005$) patient groups. Levels of sE-selectin in the sera of hepatosplenic patients (35.4 ± 3.2 ng/ml) were not different from those of control patients. In contrast to the sICAM-1 data, high-egg-excreting and low-egg-excreting patient group sE-selectin levels did not differ from each other (Fig. 2A). Also, although the sE-selectin levels of intestinal and hepatosplenic patient groups were significantly different ($P = 0.005$), the intestinal group had the higher sE-selectin levels (Fig. 2B), while the hepatosplenic group had the higher sICAM-1 levels (Fig. 1B). Again, there were no correlations between sE-selectin levels and other parasitic infections (data not shown).

Relationship of sICAM-1 and sE-selectin levels. Because many of the cytokines which upregulate ICAM-1 expression also upregulate E-selectin expression (5, 6, 17, 37), regression analyses comparing sICAM-1 and sE-selectin levels in patient sera were performed (Fig. 3). Interestingly, there was a strong positive correlation of sICAM-1 and sE-selectin levels in the sera of high- and low-egg-excreting patient groups ($r = 0.572$, $P = 0.0001$) (Fig. 3A), but no relationship was found between serum sICAM-1 and sE-selectin levels of intestinal and hepatosplenic patients ($r = 0.078$, $P = 0.5514$) (Fig. 3B). This lack of correlation was attributable primarily to the effects of the hepatosplenic group. When the sICAM-1 and sE-selectin levels were compared for the intestinal patients alone, there was a significant correlation ($r = 0.400$, $P = 0.035$ [data not shown]).

TNF-α levels in patient sera. TNF-α induces expression of both ICAM-1 and E-selectin (5, 6, 37), effects release of ICAM-1 and E-selectin from cells (2, 40), seems to be important for granuloma formation in schistosomiasis (1, 13, 27), and has been shown to be elevated in the sera of schistosomiasis patients (58). Therefore, the level of this cytokine was measured in patient sera to determine if it was associated with the elevated sICAM-1 and/or sE-selectin levels seen in the sera of these patients. Very few patients had appreciable levels of TNF-α in their sera (data not shown). The patients who did have elevated TNF-α in their sera did not fall into any particular clinical group or have exceptionally high sICAM-1

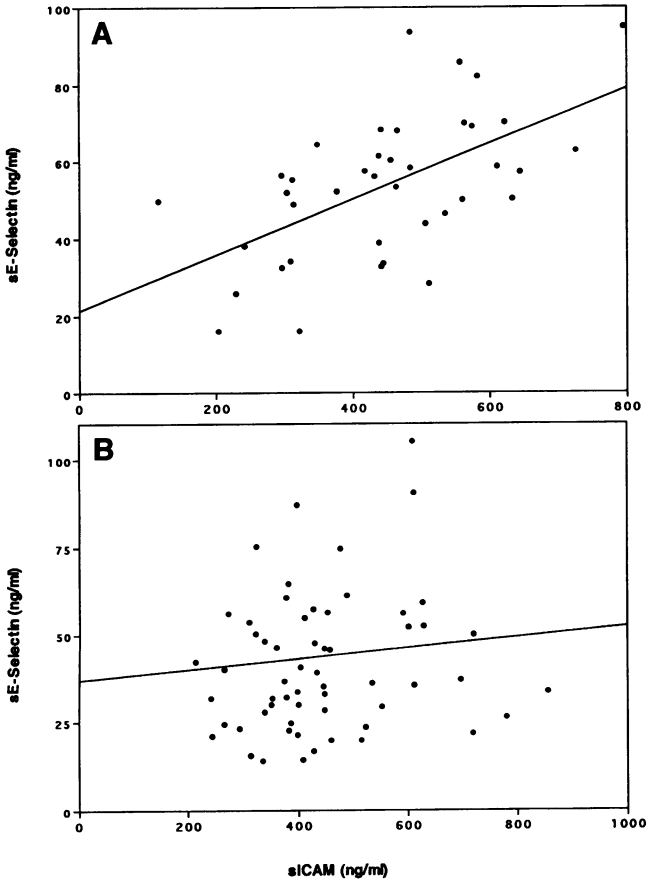

FIG. 3. Correlative analysis of sICAM-1 and sE-selectin serum levels. Simple regression analysis was performed to establish the correlation between serum sICAM-1 and sE-selectin levels in high- and low-egg-excreting (A) and intestinal and hepatosplenic (B) patient groups. There was a significant correlation between serum sICAM-1 and sE-selectin levels in high- and low- egg-excreting groups (r = 0.572, P = 0.0001) but no correlation between serum sICAM-1 and sE-selectin in intestinal and hepatosplenic patient groups (r = 0.078, P = 0.5514).

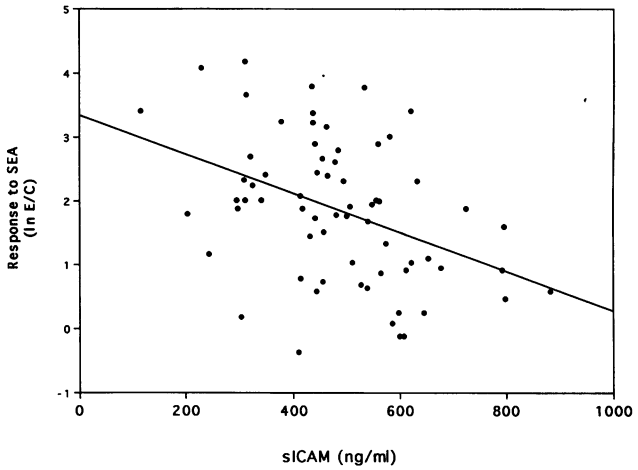

FIG. 4. Negative correlation of serum sICAM-1 levels and PBMC proliferative responses to SEA. Proliferation assays were performed as described in Materials and Methods. Proliferation data are expressed as the natural log of experimental cpm divided by control cpm (ln E/C) of incorporated tritiated thymidine and are plotted against the serum sICAM-1 level for each patient. The line represents a simple regression analysis line of best fit in which r equals 0.408. This analysis indicates a significant inverse relationship between sICAM-1 level and proliferative response to SEA with a P value of 0.0006. Spearman rank correlation analysis also indicates a significant relationship with a P value of 0.0011.

or sE-selectin levels. Thus, serum concentrations of TNF-α did not appear to correlate with clinical form, sICAM-1 levels, or sE-selectin levels in schistosomiasis. However, these measurements were made on serum samples from peripheral blood, and it has been suggested that peripheral blood TNF-α levels may not be a true reflection of portal blood or visceral tissue TNF-α bioactivity (1, 54) since TNF-α-producing cells may be sequestered from the circulation of schistosomiasis patients (58).

Proliferative response to egg antigens negatively correlates with sICAM-1 level. High- and low-egg-excreting patient sICAM-1 levels were compared with PBMC proliferative responses to schistosome antigens, purified protein derivative, and the mitogen phytohemagglutinin. Hepatosplenic and intestinal patients were not included in the comparison as most hepatosplenic patients were antigen nonresponsive. A significant negative correlation existed between sICAM-1 levels and the proliferative response (E/C) to egg antigens (r = 0.367, P = 0.0023 [data not shown]). Standardized residual analysis indicated greater E/C variances at lower sICAM-1 levels than at higher sICAM-1 levels, signifying that the relationship between the proliferative response and the sICAM-1 level may be better described by a nonlinear equation. Natural logarithmic transformation of proliferative responses (ln E/C) maintained a significant negative correlation with sICAM-1 levels (Fig. 4) and improved the linearity of the regression curve (r = 0.408, P = 0.0006). Nonparametric Spearman rank coefficient analysis (which is not affected by the form of the equation) of the data also demonstrated that this relationship was significant (rho = −0.410, P = 0.0011). The relationship between sICAM-1 levels in sera and proliferative responses to SEA was also significant if the data were expressed as E − C (r = 0.259, P = 0.0389) or ln(E − C) (r = 0.385, P = 0.0017; by Spearman analysis, rho = −0.374, P = 0.003). The inverse relationship seen between sICAM-1 levels and the proliferative response was not due to variations in the control responses since control thymidine incorporation did not alter with changes in sICAM-1 levels (r = 0.01, P = 0.934 [data not shown]). Responses to other schistosome antigens, purified protein derivative, and phytohemagglutinin had no relationship to sICAM-1 levels (data not shown). Regression analyses comparing the relationship between sE-selectin levels and proliferative responses of high- and low-egg-excreting individuals were also performed. There were no significant correlations between sE-selectin levels and any PBMC stimulant used (data not shown). Therefore, the relationship between sICAM-1 level and PBMC response to SEA was the only significant relationship that existed between PBMC proliferation and serum adhesion molecule concentration.

DISCUSSION

This study demonstrates elevated levels of soluble intercellular adhesion molecules in the sera of schistosomiasis patients. Compared with never-infected control individuals, sICAM-1 levels are elevated significantly in sera from adult patients with hepatosplenic and intestinal forms of disease as well as younger patients (whose final disease form is not yet

evident) excreting either high or low numbers of eggs in their feces. Also, patients with relatively more-severe disease (hepatosplenic and high-egg-excreting patients) have significantly higher levels of sICAM-1 in their sera than patients with milder disease forms (intestinal and low-egg-excreting patients). Most likely, elevated sICAM-1 levels are a result of the inflammatory responses leading to granuloma formation, with higher sICAM-1 levels in severe disease forms reflecting the more intense inflammation which may be occurring in these patients. Soluble ICAM-1 levels are similarly related to disease severity in patients with primary biliary cirrhosis (53) and Hodgkin's disease (41).

Levels of sE-selectin are also significantly elevated in the sera of schistosomiasis patients with most forms of the disease compared with those of never-infected control individuals. In contrast to sICAM-1, however, sE-selectin is not significantly elevated in patients with hepatosplenic disease. In addition, the difference in serum sE-selectin levels between high- and low-egg-excreting individuals is not significant. Regression analysis indicates a significant correlation between sICAM-1 and sE-selectin levels in sera from intestinal and high- and low-egg-excreting individuals but not in sera from hepatosplenic patients. This suggests that, although ICAM-1 and E-selectin are upregulated by many of the same mechanisms (5, 6, 17, 37), their in vivo regulation is not absolutely coordinated and that hepatosplenic patient cells may be expressing adhesion molecules and releasing them by a different mechanism than cells from patients in the other groups.

The most intriguing finding of this study is the inverse correlation between sICAM-1 levels in sera and PBMC proliferative responses to egg antigens. Patients with chronic intestinal schistosomiasis have lower proliferative responses to egg antigens than patients who have acute disease; however, responses to other schistosome antigens remain elevated (12, 22). Many hypotheses have been proposed for this specific immunoregulation of PBMC proliferative responses to egg antigens, but the definitive cause(s) remains undetermined. While the explanation for this phenomenon may be as simple as a sequestration of the SEA-reactive T cells in granulomas, it is interesting to consider the potential significance of the relationship between sICAM-1 levels and proliferative responses. One possibility is that elevated levels of soluble adhesion molecules may simply be a by-product of cellular damage caused by parasite ova. Patients with more cellular damage would have higher sICAM-1 levels because cellular ICAM-1 would be released during cell destruction and fragmentation. A lowered responsiveness to antigenic stimulation would also occur if cells necessary for antigen presentation and/or response were damaged by the parasite. However, such a generalized phenomenon would apply to the response to any antigen or mitogen stimulation (and, therefore, may be the case with the decompensated hepatosplenic patients in this study) and would not explain the apparent specificity for egg antigens. Also, studies have demonstrated that cytokine-activated cells with no apparent damage release adhesion molecules (40). In addition, both sICAM-1 and sE-selectin are released as single polypeptides and retain their ligand specificities (2, 40, 43); this would be unlikely if their release were caused by membrane fragmentation (40).

A second potential explanation for the correlation between increased sICAM-1 levels and decreased proliferative responses would be that cytokines important for granuloma modulation (and decreased proliferation to egg antigens) concurrently induce cellular release of sICAM-1 and that no cause-and-effect relationship exists between sICAM-1 level and the proliferative response. In fact, IFN-γ, which has been shown to trigger release of sICAM-1 from cultured cells (2, 40), is correlated with granuloma modulation (32). However, these findings do not exclude the possibility that IFN-γ triggers the release of ICAM-1 and that the sICAM-1 serves as the actual modulator rather than the IFN-γ. Although specific experiments to define the relationship of IFN-γ, sICAM-1, and proliferative response levels would be interesting to perform, this hypothesis also does not explain the apparent antigenic specificity of the modulated response.

Two related theories that do address the antigenic specificity of the modulated response focus on egg antigen presentation in or near the granuloma microenvironment. Efficient antigen presentation to T cells requires the participation of costimulatory molecules; inappropriate costimulation leads to unresponsive or anergic responder cells (8, 36, 45, 51). Several studies have demonstrated that ICAM-1 has an important costimulatory role in T-cell activation (9, 15, 20, 28, 35, 44, 55). Tissue culture wells coated with anti-CD3 antibody and ICAM-1 stimulate proliferation while wells coated with anti-CD3 alone do not (28, 55). Likewise, cells transfected with both major histocompatibility complex molecules and ICAM-1 are much more efficient antigen-presenting cells than cells transfected with major histocompatibility complex molecules alone (20, 28). Also, ICAM-1 knockout mice have a reduced ability to mount delayed-type hypersensitivity responses and are poor stimulators for mixed lymphocyte reactions (57). Therefore, if granuloma or draining lymph node antigen-presenting cells shed ICAM-1 (perhaps in response to IFN-γ or TNF-α), they may not express the levels of cell surface ICAM-1 necessary for efficient costimulation of SEA-specific T cells.

Alternatively, the shed ICAM-1 could block costimulation by competitively binding leukocyte function-associated antigen 1 (LFA-1) on T cells and thereby blocking the interaction of cellular ICAM-1 with its ligand. Peptide analogs of ICAM-1 (18) or antibodies against ICAM-1 or LFA-1 (9, 15, 20, 28, 35, 55) lead to reduced or abrogated T-cell responses. Recombinant soluble ICAM-1 blocks the ability of rhinovirus to infect susceptible cells, albeit only at levels which are higher than serum concentrations, even in disease states (33). However, much lower (physiologic) concentrations of purified natural ICAM-1 block natural killer cell or lymphokine-activated killer cell cytotoxicity for melanoma cell lines by inhibiting the ICAM-1–LFA-1 interaction (2, 3). Even if very high concentrations of sICAM-1 are necessary to competitively inhibit cellular ICAM-1–LFA-1 interactions, it is possible that the microenvironment in which egg antigen presentation is occurring would have higher concentrations than that present in peripheral serum.

If either or both of these mechanisms of reduced costimulation occur in the granuloma or draining lymph node microenvironment, they would potentially lead to inappropriate presentation of egg antigens (but not antigens outside the granuloma) and the observed reduction in T-cell responsiveness specific for egg antigens. Consequently, sICAM-1 released through the granuloma inflammatory response could provide a mechanism for feedback control of SEA-specific T-cell responsiveness, resulting in granuloma modulation. This theory remains highly speculative and circumstantial with the limited current data concerning intercellular adhesion molecules in schistosomiasis. However, with the recent demonstration of elevated ICAM-1 expression associated with acutely forming granulomas in murine schistosomiasis (42) and the data derived from this study, cell surface and soluble adhesion molecules may participate in regulating the pathology associated with schistosomiasis.

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