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MINIREVIEW

Regulation of Granulomatous Inflammation in Experimental Models of Schistosomiasis

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Schistosomiasis is a parasitic disease affecting more than 200 million people. Its major pathology is granulomatous inflammation, a cellular immune response to antigens secreted by schistosome ova. The murine models of this disease have been widely studied because they permit a variety of genetic and other experimental approaches. The murine infections differ from the human, monkey, and baboon infections in many ways, especially in the number of adult worms per unit of body weight and the distribution of ova between the liver and mesenteric circulation. However, all of these species develop hepatic granulomatous (HG) inflammations that have similar dynamics and cellular compositions and are spontaneously downmodulated. Therefore, knowledge about the mechanisms of regulation of these inflammations in the mouse models is relevant to the other species. Most of the available evidence is related to HG inflammation resulting from infection with cercariae. In occasional studies workers employ another model, pulmonary granulomas (PG) induced by injection of ova or beads coated with schistosomal egg antigens (SEA) into naïve or schistosome-infected mice.

This review differs from previous reviews of this disease in that it synthesizes relevant older and newer studies into a sequence of microenvironmental, cellular, molecular, and immunological events resulting in granuloma formation and eventually downregulation. It also presents different viewpoints and new questions about some controversial and/or confusing subjects, including mechanisms of regulation by Th1- and Th2-type cytokines, chemokines, and other types of molecules and their receptors; signal transduction pathways; different types of regulatory cells; the role of gut-associated lymphoid tissue (GALT), B cells, and Fc gamma receptors (FcγR); and finally, the balance between T effector (T_E) and T regulatory (T_R) cells in the control of immunity and pathology.

SCHISTOSOME LIFE CYCLE

Schistosomiasis is an ancient and chronic disease of humans, nonhuman primates, other mammals, and birds that is caused by a number of species of flatworms (Platyhelminthes). In this review I focus on the murine model diseases caused by two major human pathogens, *Schistosoma mansoni* and *Schistosoma japonicum*. The mammalian host is infected during contact with freshwater contaminated with infectious cercariae produced by various species of snails. The cercariae penetrate intact skin and through a series of morphological, membrane, biochemical, and antigenic changes transform into schistosomulae. After days in subcutaneous tissue, the somulae travel to the lung, where they undergo adaptations for intravascular migration. From the lung the somulae are distributed to all organs. Most somulae eventually reach the liver, where they attain sexual maturity and enter the portal venous system. The adult worms mate and then travel to the small mesenteric venules. The females release ova, which migrate though the venule wall, the lamina propria, and the gut epithelium into the lumen and ultimately to the outside environment with the feces. (The embryos in the ova, the miracidia, are released and infect snails, in which they develop into infectious cercariae.) Some ova are retained in local tissues, but others go to the portal system, where they lodge in the sinusoids and induce HG. In infected mice about 75% of the ova are in the liver and the rest are in other tissues, including the mesentery (143).

GENETIC CONTROL OF CELLULAR AND HUMORAL IMMUNE RESPONSES

Table 1 summarizes experiments which examined genetic control of various parameters of cellular and humoral immune responses. These experiments showed that there is H-2 genetic control of epitope recognition (6, 56), the antibody response (7, 74), and development of Th1 and Th2 cytokine-expressing subsets (7), but there is non-H-2 control of HG size, portal hypertension, and fibrosis (20, 21, 36, 43). The apparent discrepancy between the H-2 gene control of Th1-Th2 subset development and the non-H2-control of granulomatous inflammation, which is $CD4^+$T cell dependent, remains to be explained.

GRANULOMA FORMATION

Dynamics of involvement of different microenvironments, cell populations, cellular activation, differentiation, and expansion. SEA-reactive major histocompatibility complex class II (MHC-II)-bearing $CD4^+$ ($\alpha\beta^+$) T memory-effector ($T_{M/E}$) cells are required for HG formation in mice (5, 62, 90). During the early weeks of an infection, T-lymphocyte activation and $T_{M/E}$ cell expansion and differentiation required for HG formation occur in extrahepatic microenvironments, including

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TABLE 1. Genetic control of immune responses in schistosomiasis

Parameter	Genetic loci	Observation(s)	Reference(s)
Epitope recognition	H-2	C3H and CBA Th cells show strong responses and C57BL/6 Th cells show a weak response to Sm-p40, a major SEA immunogen	56
		Opposite responses by these cells to 62-kDA SEA component	6
Antibody response	H-2	Different levels of antibody responses to different SEA immunogens in different mouse strains	74
Cellular immune responses	H-2	Th1-Th2 subset development differed in different mouse strains	7
	Non-H-2, more than one gene	HG size, fibrosis, and portal hypertension different in different mouse strains	20, 21, 36, 43

bronchial, mediastinal, and hepatic lymph nodes (LN) and the spleen, where somulae and their antigens are present (75, 76). Activation, expansion, and differentiation of SEA-reactive $B_{M/E}$ cells culminating in antibody formation also occur in these extrahepatic lymphoid sites (75, 76) and mucosal tissues (38). Somular antigens which cross-react with SEA (85) must induce this early development and expansion of SEA-reactive lymphocytes. Thus, in a mouse 4 weeks postinfection, when egg laying begins and several weeks before HG appear, SEA-reactive lymphocytes are primed and proliferate in the spleen (78). These SEA-reactive lymphoblasts are then recruited into the HG (121).

Baboons infected by a single exposure to cercariae of *S. mansoni* developed HG whose size and eosinophilia peaked 6 weeks after infection (44). After multiple cercarial exposures, HG size and eosinophilia peaked at 9 weeks. In both groups the size of the HG diminished by week 13, but downsizing occurred more rapidly in the baboons with multiple cercarial exposures (44).

Granulomas also develop in the intestines of schistosome-infected mice. The granuloma sizes in the liver, colonic mucosa, and ileal Peyer's patches peak 8 weeks postinfection and then spontaneously decrease (143). There are differences in cellular composition; HG contain the largest number of T and B lymphocytes, eosinophils, and mast cells, whereas ileal granulomas consist mainly of macrophages (145). There are different patterns of distribution of T and B lymphocytes within granulomas in different tissues (145).

Roles of costimulatory, adhesion, and chemokine molecules. The binding of costimulatory B7 ligands on antigen-presenting cells to CD28 receptors on T cells can enhance activation and proliferation of T lymphocytes (54). B7-2 expression by HG cells in *S. mansoni*-infected mice has been implicated in early T-lymphocyte activation, expansion, and differentiation because it was elevated 6.5 weeks postinfection (113). B7-2 was also involved in PG formation elicited by injection of ova; anti-B7-2 treatment greatly inhibited this process (133). However, HG size was not significantly different in *S. mansoni*-infected B7-1, B7-2, or double knockout (KO) and wild-type (WT) mice (57), suggesting that there is only a marginal requirement for B7-1 and B7-2 molecules. The significance of elevated expression of B7-1 and CD40 by splenic $CD8\alpha^+$ dendritic cells (DC) 8 weeks after *S. mansoni* infection (132) remains to be assessed.

Antibodies to the adhesion molecules intercellular adhesion molecule 1 (ICAM-1), lymphocyte function-associated antigen 1 (LFA-1), and very late antigen 4 (VLA-4) inhibited proliferation and interleukin-2 (IL-2) and IL-4 production by splenic and HG lymphocytes of acutely infected mice (82). Injection of SEA-coated Sepharose beads into *S. mansoni*-infected mice stimulated expression of ICAM-1, LFA-1, VLA-4, and VLA-6 around HG, suggesting that these adhesion molecules participate in initiation and maintenance of HG (64). Eight weeks postinfection ICAM-1, LFA-1, and VLA-4 were upregulated in ileal colonic granulomas, and syndecan 1 immunoreactive B lymphocytes were present close to SEA-laden macrophages in inner areas of ileal and colonic granulomas (65).

The numbers of adult worms in *S. japonicum*-infected mast cell-deficient mice were similar to the numbers in WT mice, but the HG size was significantly reduced in the former mice (105). The reduction was attributed to deficient production of eosinophil chemotactic factor. The levels of chemokine monocyte chemoattractant protein 1 (MCP-1) mRNA and protein were increased in PG induced by injection of *S. mansoni* ova into infected or noninfected mice (33). MCP-1 expression was greatest within microvascular adventitial cells or pericytes, as well as mononuclear cells associated with PG. Injection of antibodies to MCP-1 inhibited PG formation. MCP-1 was expressed in HG and branches of the hepatic artery in *S. mansoni*-infected mice inoculated with SEA-coated beads (64). The chemokine macrophage inflammatory protein 1α (MIP-1α) was identified in macrophages in primary PG (86). Treatment with antibody to MIP-1α decreased PG formation. When schistosome ova were injected into infected mice, there were distinct coordinated patterns of chemokine expression in the liver and draining LN (107).

Cytokines and chemokine effects were interrelated. Thus, neutralization of tumor necrosis factor alpha (TNF-α) by antibody inhibited chemokine production by pulmonary cells (111). The level of monocyte chemotactic protein 3, which binds to CCL7 receptor, was elevated by IL-4, and monocyte chemotactic protein 3 contributed to eosinophil recruitment (124).

Cytokines. The Th1 and T-cytotoxic 1 T-cell subsets produce type 1 cytokines (IL-2 and interferon gamma [IFN-γ]), whereas the Th2 and T-cytotoxic 2 T-cell subsets produce type 2 cytokines (IL-4, IL-5, and IL-10) (99, 100). Eight weeks after *S. mansoni* and *S. japonicum* infection Th2-type cytokine production by spleen cells (SC) and HG cells was predominant compared with Th1-type cytokine production (37, 55, 151). There appeared to be cross-regulation of cytokine production:

TABLE 2. Regulation of HG inflammation in murine schistosomiasis by injection of antibodies to cytokines and cytokine receptors

Species	Antibody specificity	Effects on granulomas			Reference
		Size	Cellular composition	Fibrosis	
S. mansoni	IL-2	Decrease	Eosinophils decrease		22
S. mansoni	IL-4	None		Decrease	26
S. japonicum	IL-4	Increase		Decrease	23
S. japonicum	IL-5	Decrease		None	25
S. mansoni	IL-5	None	Eosinophils decrease	None	125
S. mansoni	IL-10	Increase	Eosinophils increase		40
S. mansoni	IL-10	Increase	Eosinophils increase		15
S. mansoni	IFN-γ	None	Eosinophils increase	None	125
S. japonicum	IFN-γ	Decrease		None	28
S. mansoni	TNFα	Decrease			71
S. mansoni	IFN-γ receptor	Decrease	Decrease in epithelioid cells		118
S. mansoni	IL-2 receptor	None		None	22
S. japonicum	IL-2 receptor	Increase	Decrease in eosinophils	None	27

as Th2 cytokine production increased, Th1 cytokine production decreased (55, 126, 151).

These observations led to the prevalent dogma that Th2-type cytokine expression is predominant and is correlated with HG formation and that increased Th2 cytokine production is accompanied by reduced Th1 cytokine production. However, this view was challenged (78) because it was largely based on in vitro cytokine production by exogenous SEA-stimulated SC, ex vivo cytokine production induced by endogenous SEA was not examined, and the comparative dynamics of ex vivo cytokine responses of SC and HG cells to endogenous SEA also were not examined. Moreover, based on a previous study (95), it was predicted that exogenous SEA would dynamically and quantitatively alter the cytokine responses of SC and HG cells. Thus, the previously observed Th2 cytokine-dominated responses to exogenous SEA might have been skewed compared to the responses induced by endogenous SEA and, therefore, would not be expected to correlate with HG formation.

The validity of this challenge and these predictions was supported by the results of a study (78) in which the ex vivo endogenous SEA-induced cytokine responses by SC and HG cells were dynamically and quantitatively different from the responses stimulated by exogenous SEA. Unexpectedly, SC and HG cell responses were also dramatically different. Ex vivo HG cells showed a >10-fold-greater frequency of IL-4-, IL-5-, and IFN-γ-secreting HG cells than SC. Eight weeks postinfection HG cells ex vivo secreted much higher concentrations of IL-4 and IL-5 but much lower concentrations of IFN-Y than SC secreted. Endogenous SEA induced HG cells to produce much larger amounts of IL-4, IL-5, and IL-10 than SC produced. The ex vivo responses were better correlated with the dynamics of HG formation than the exogenous SEA-stimulated responses were. Whereas exogenous SEA induced SC to produce larger amounts of cytokine, exogenous SEA downregulated cytokine production by HG cells (78), confirming previous findings (95).

Endogenous SEA-evoked ex vivo and constitutive cytokine expression (both numbers of cytokine-producing cells and amounts of cytokine produced) by $CD4^+$ SC preceded cytokine expression by $CD4^+$ HG cells and was coordinate (78). The data are compatible with the development of SEA-reactive cytokine-producing cells in the spleen and the subsequent migration of these cells into liver (78, 121).

Table 2 shows the effects on HG size of introduction during infection of blocking antibodies to some cytokines and cytokine receptors. By this criterion, IL-2 (22), TNF-α (71), and the IFN-γ receptor (119) in *S. mansoni*-infected mice and IL-5 (28) and the IL-2 receptor (27) in *S. japonicum*-infected mice participated in HG pathogenesis. In *S. mansoni*-infected mice IL-2 (22), IL-5 (125), IL-10 (15, 40), IFN-γ (125), and the IFN-γ receptor (119) and in *S. japonicum*-infected animals the IL-2 receptor (27) were also involved in determining the cellular composition of the HG.

Table 3 shows that the introduction during infection of some recombinant cytokines, including recombinant IL-2 (91), recombinant IL-7 (146), and recombinant TNF-α (3, 71), enhanced HG size. Recombinant TNF-α occasionally did not restore HG formation (24), suggesting that this cytokine was only marginally required.

Table 4 shows that infected mice with KO of some genes for

TABLE 3. Regulation of granulomatous inflammation by injection of recombinant cytokines

Cytokine	Injection schedule and/or recipients	Effects on granulomas	Reference
IL-2	Daily during acute or chronic infection	Increase HG size	91
IL-7	Before infection	Increase HG size, fibrosis	146
IL-10	4 to 8 weeks postinfection; mice receiving ova intravenously	Decrease PG size	48
IL-10Fc	4 to 8 weeks postinfection	Decrease HG size	48
TNF-α	SCID mice	Restore HG size	2
TNF-α	During chronic infection	Increase HG size	71
TNF-α	SCID mice	None on HG	24
IL-12	Mice receiving ova intravenously	Decrease PG size	150
IL-12	Daily 5 to 7.5 weeks postinfection	Decrease HG size, fibrosis	16

TABLE 4. Regulation of HG inflammation in mice with deletions of genes for T and B cells, cytokines, and Fcγ and substance P receptors

Deletion genes	Effects on granulomas				
	Acute	Downregulation	Cellular composition	Fibrosis	Reference
B cell	Increase			Increase	47
B cell	Increase	Abolished		Increase	67
$CD8^+$ T	None	None		None	154
SCID	Decrease				2
IL-4	Decrease		Fewer eosinophils, no mast cells		95
IL-10	Increase	None			149
IL-13	None		None	Decrease	42
IL-4/IL-13	Decrease		Fewer eosophils	Decrease	42
IFN-γ				None	2
IFN-γ	None	None		Decrease	154
IL-4α receptor	Decrease				70
IFN-γ receptor	None		None	None	1
IFN-γ receptor	Decrease		Reduction of infiltrating cells		118
IFN-γ receptor	Decrease		More immature, proliferating monocytes	Increase	104
FcεR	Increase			Increase	68
FcγR	Increase	Abolished			68
Substance P receptor	Decrease		None		11

cytokines and cytokine receptors developed smaller HG than WT mice developed, implicating IL-4 (95), the combined effects of IL-4 and IL-13 (42), and the IL-4α (70) and IFN-γ (104, 118) receptors in HG pathogenesis. On the other hand, deletion of the IL-13 gene did not affect this process (42).

Additional evidence further dissociated the Th2 cytokine and HG responses (81). Eight weeks after mice deficient in the third component (C3) of complement were infected with *S. mansoni*, SEA-specific Th2 cytokine (IL-5, Il-6, IL-10, IL-13) production by the SC was significantly reduced. Nevertheless, the HG sizes in WT and C3 KO mice were indistinguishable. It was not determined whether the cellular compositions of the HG were similar or different in the WT and deficient mice.

In summary, diverse evidence strongly implicates both Th1 cytokines (IL-2, IFN-γ) and a Th1 cytokine receptor (IFN-γ) and Th2 (IL-4, IL-4–IL-13, IL-5, TNF-α) and a Th2 cytokine receptor (IL-4α) in determination of HG size. Evidence obtained by King et al. (78) and the failure of the granulomatous response to switch to Th1 in IL-4-deficient mice (95) indicate that cross-regulation of the Th1 cytokine response by Th2 cytokines does not occur. Other data show that the Th1 and Th2 cytokine responses are interdependent: the IL-4 response influences the IL-2 response (153), and IL-2 contributes to the IL-5 response (96). There is also evidence (Tables 2 and 4) that Th1 cytokines (IL-2, IFN-γ) and a Th1 cytokine receptor (IFN-γ) and Th2 cytokines (IL-4, IL-5) are involved in determination of the cellular composition of the HG.

Signal transduction pathways. Mice with deletions of signal transducer and activator of transcription 4 (STAT4) and STAT6, involved in signal transduction pathways for Th1 and Th2 cell development, respectively, were inoculated with ova or infected with cercariae of *S. mansoni.* Seven weeks later they were inoculated intravenously with ova and then sacrificed 8 days later (73). In the group inoculated with ova the PG size was reduced significantly in the STAT6 KO mice but not in the STAT4 KO mice. In the the group inoculated with infected ova the HG and PG sizes were reduced in the STAT6 KO mice but not in the STAT4 KO mice. Therefore, Th2 cytokines, but not Th1 cytokines, appeared to be required for egg-elicited HG and PG formation. However, the relevance of STAT4 and STAT6 to HG formation was not established because infected mice were also inoculated with ova.

SC or mesenteric LN from infected STAT6 or IL-4α receptor KO mice produced low levels of IL-4 and IL-5 compared to the levels produced by WT mice (69, 73). Mesenteric LN from these mice also had smaller numbers of $CD4^+$ T cells producing these cytokines, suggesting that IL-4 and STAT6 signaling determined the Th2 cell frequency but were not essential for Th2 cell differentiation. The HG from these mice made IL-4 or IL-5, but their T cells produced only small amounts of IFN-γ (94).

Signals through the T-cell receptor (TCR) and cytokine receptor initiate Th1 cytokine expression via STAT4 and induction of transcription factor T-bet (116). Signals that activate STAT6 induce transcription factor GATA3, leading to Th2 cytokine expression. Coordinate Th1 and Th2 cytokine expression in the spleen and HG (78) might result from simultaneous triggering of the Th1 and Th2 cytokine pathways in different $CD4^+$ T-cell populations by different egg antigen epitopes (17), reflecting the great heterogeneity of the TCR repertoire (59). Greater production of IL-4, IL-5, and IL-10 suggests that there is greater expression of GATA3 by HG than by SC. Greater production of IFN-γ by SC indicates that there is greater expression of T-bet by SC. Simultaneous expression of Th1 and Th2 cytokines by both SC and HG cells suggests that both transcription factors are produced by different populations of SEA-specific $CD4^+$ T cells.

Neuropeptides. As shown in Table 4, infection of mice with deletion of the substance P receptor decreased HG size, involving this receptor and, by association, its ligand, substance P, in HG formation (11).

Cellular requirements. HG formation is initiated by delayed-type hypersensitivity (DTH) mediated by SEA-reactive $CD4^+$ ($\alpha\beta^+$) MHC-II-dependent T cells (5, 59, 90). The gene KO experiments (Table 4) showed that HG formation does not require $CD8^+$ T cells (154) or B cells (47, 67). Another study showed that B cells are required for Th2 cytokine responses but not for HG formation (58).

Consistent with the requirement of $CD4^+$ T lymphocytes for HG formation, cytokines whose expression correlated with HG size were produced by $CD4^+$ T cells in the spleen and HG (78). However, in contrast to the spleen, where the IL-4- and IL-5-producing cells were all $CD4^+$ T cells, about 50% of the HG cells secreting these cytokines were $CD4^+$ T cells (78). IL-4 and IL-5 are produced by cells other than $CD4^+$ T cells, including NK cells (101), $CD8^+$ T cells (109), γ/δ cells (115), activated eosinophils (120), basophils (41), and non-B, non-T cells (123). HG cells produce other cytokines implicated in HG pathogenesis, including IL-10 (95), TNF-α (13, 84), and transforming growth factor β (TGF-β) (13).

HG formation could be initiated by a few T cells recruited to the liver that then expand locally or by T cells that are activated and expanded and whose receptors (TCR) are diversified extrahepatically and then home into the hepatic DTH inflammatory site induced by ova. The finding that the TCR repertoire of a single HG was very diverse indicated that most of the T cells recruited to these lesions were activated and expanded and that their TCR repertoire was diversified in extrahepatic microenvironments (59). This study also showed that some non-SEA-specific T cells homed into the HG.

IgE. HG size was significantly decreased in IgE-deficient SJA/9 mice compared to the HG size in C57BL/6 or SJL/J mice infected with *S. japonicum* (106). In another study *S. mansoni*-infected mice from which the immunoglobulin E (IgE) gene was deleted developed smaller HG despite increased worm burdens (77). This effect was attributed to IgE-mediated activation of mast cells, which are present in HG, leading to release of inflammatory mediators and cytokines that promote HG formation. However, inasmuch as infected FcεR KO mice develop larger HG than WT mice develop (68), immune complexes (IC) of IgE antibody and SEA might react with FcεR on various cells to promote HG formation by as-yet-undetermined pathways.

FIBROSIS

Fibrosis develops in granulomas during the chronic phase of granulomatous inflammation in murine schistosomiasis. A variety of molecules stimulate the differentiation of stellate cells into myofibroblasts that secrete extracellular matrix proteins, including collagens, fibronectin, and glycosaminoglycans. Fibrogenesis is a dynamic process regulated by cytokines produced by macrophages, lymphocytes, and fibrocytes (34, 147). Experiments performed with antibodies to cytokines (Table 2) implicated IL-4 in upregulation of fibrosis (23, 26). Injection of recombinant cytokines (Table 3) resulted in association of IL-12 with upregulation of this process (16). KO experiments (Table 4) inconsistently implicated IFN-γ (2, 154) in fibrosis.

TGF-β is associated with hepatic fibrosis based on a variety of evidence. Treatment of cultured hepatic cells with TGF-β1 increased the level of type I procollagen mRNA, and an increase in TGF-β1 gene expression preceded the increase in collagen synthesis (39). This cytokine was present in normal mouse hepatocytes, and the levels were markedly increased in schistosome-infected mice at the periphery of HG and on Kupffer cells in parenchyma (39). At this time deposition of heparan sulfate proteoglycan within the HG was prominent.

Peripheral blood fibrocytes produce type I collagen, and HG in *S. japonicum*-infected mice contain fibrocytes in areas where there is connective tissue matrix deposition, suggesting that these cells contribute to fibrosis (34).

There is diverse evidence that regulation of HG fibrosis is independent of the regulation of HG. Thus, the degree of HG fibrosis was unrelated to HG size in a number of *S. japonicum*-infected mouse strains (20). Injection of antibody to IL-4 increased HG size but decreased fibrosis in mice infected with *S. japonicum* (28). Splenectomy of *S. mansoni*-infected mice 8 weeks postinfection enhanced HG formation but did not affect fibrosis (60). Adoptive transfer of SC from mice chronically infected with *S. japonicum* into acutely infected mice reduced the portal pressure and HG size but did not affect fibrosis (102). Finally, TGF-β promoted fibrosis (39), but its appearance correlated with a decrease in HG size (97, 139).

DOWNREGULATION OF GRANULOMATOUS INFLAMMATION

Correlation with expression of costimulatory, adhesion, prostaglandin, and cytokine molecules. Expression of the costimulatory molecule B7-2 was enhanced during the acute phase but was sharply diminished concurrent with a decrease in HG size (113). On the other hand, MHC-II expression by HG cells was constant throughout murine *S. mansoni* infection (113). HG were enlarged in mice inoculated daily with a monoclonal antibody to inducible costimulatory molecule (ICOS) for 3 weeks beginning 4 weeks postinfection (122). ICOS is associated with antigen-primed T cells, binds B7-related protein 1 (B7RP-1), and regulates the differentiation of $CD4^+$ T cells (92). Injection of antibody to ICOS results in a great increase in IFN-γ production by SEA-stimulated HG, mesenteric LN, and purified $CD4^+$ T cells. These observations link the ICOS–B7RP-1 pathway to downregulation and IFN-γ to upregulation of HG formation.

The dynamics of ex vivo expression of IL-2, IL-4, IL-5, and IFN-γ by SC and HG cells correlated with the formation and downmodulation of HG (78). Infection of IL-10 KO mice (Table 4) (149) and injection of antibodies to IL-10 (Table 1) (15) increased HG size. On the other hand, injection of IL-10 and IL-10:Fc (49) and IL-12 (16, 150) reduced PG size.

Administration of prostaglandin E1 inhibited PG formation (31). Macrophages from mice infected for 8 weeks constitutively produced prostaglandins (31). Injection of methyl prostaglandin E1 into infected mice resulted in general immunosuppression, including reduced HG and PG size, splenomegaly, B-cell proliferation, and IL-2 production (32).

Downregulation of the proliferative response. Splenic T-cell proliferation and HG downregulation decreased concurrently in chronically infected mice (50, 78, 112, 152).

Role of neuropeptides. HG eosinophils produce vasoactive intestinal peptide, and HG T lymphocytes have vasoactive intestinal peptide receptor (96). Vasoactive intestinal peptide decreased SEA-induced T proliferation and $CD4^+$ T-cell-dependent IL-2 production (96). $CD4^+$ T lymphocytes produce somatostatin, and somatostatin decreases IFN-γ secretion by SEA-stimulated cells (12). Somatostatin is a product of HG macrophages (143). These observations implicate neuropeptides and their receptors in granuloma downmodulation

through downmodulation of T-cell expansion and of production of cytokines participating in this process.

Role of B cells, macrophages, IgG1, immune complexes, and FcγR. The gene KO experiments (Table 4) indicated that B cells and FcγR, but not $CD8^+$ T cells, were required for HG downregulation (47, 67, 68, 154). HG downmodulation by B cells and FcγR could be initiated by IC of SEA and the IgA, IgE, IgG1, and IgG2a antibodies to SEA produced by B cells in the spleen, mediastinal, mesenteric, and hepatic LN and later in the HG and mucosal intestinal tissues (1, 14, 38, 68, 75, 76, 77, 95, 128). Circulating IC are present in human schistosomiasis patients (83) and presumably in mice with the disease. In sites where IC form there are FcR-bearing macrophages, DC, B cells, basophils, mast cells, and neutrophils. The IC-FcγR reactions could inhibit HG formation by generating production of immunoinhibitory molecules, such as IL-10 and prostaglandins, by one or more of these types of cells (10, 72, 117).

Alternatively, but not exclusively, the IC-FcγR reaction could inhibit inflammation by suppressing expression of surface MHC-II (138) and IL-1 (137), molecules required for antigen presentation. Thus, IC from patients with chronic intestinal schistosomiasis inhibited expression of MHC-II (histocompatibility locus antigen DR) by B cells in vitro (117).

FcγR are present on macrophages in the HG (4). The reaction of IC with FcγR IIB on macrophages inhibits a variety of immunologically induced inflammatory responses by as-yet-undefined mechanisms (114). The engagement of these receptors on cells in the HG and other tissues might downregulate production of cytokines and chemokines that participate in HG formation and fibrosis. For instance, the homing of cells into liver to form HG might be reduced by the generation of chemokines (MIP-1α, MIP-1β, RANTES) by activation of cells through their FcγR (46). When the chemokine is bound, its receptor would be internalized and, therefore, not able to mediate chemotaxis.

Injection of the IgG1 fraction of serum from mice infected for 30 weeks with *S. japonicum* into acutely infected recipients reduced the HG size and portal pressure (103). This fraction suppressed SEA-induced blastogenesis of SC from acutely infected mice (50). It is not known how IgG1 caused these effects; one possibility is binding to SEA to form IC, which induce production of immunomodulatory molecules (10, 72, 117).

Roles of regulatory T cells and non-T cells. Granulomatous inflammation was downregulated by the adoptive transfer into acutely infected animals of SC and LN cells from chronically infected mice (35). Adoptive transfer of both $CD4^+$ and $CD8^+$ cells reduced the HG size (29). $CD8^+$ cells from mice chronically infected with *S. japonicum* or *S. mansoni* suppressed SEA-stimulated cell proliferation and migration inhibitory factor and IL-2 production by SC or HG cells from acutely infected animals (112, 129, 130, 131, 144). $CD8^+$ cells also reduced the HG or PG size (103, 112).

Reduced expression of proinflammatory cytokines and increased production of immunoregulatory molecules were temporally correlated with the appearance of regulatory cells in extrahepatic and hepatic microenvironments. The T_R and other regulatory cells might reduce granuloma formation by inhibiting SEA-stimulated cell proliferation and cytokine production by SC or HG cells from acutely infected mice (50, 78, 95, 112, 129, 130, 152). Regulatory macrophages downregulated proliferation by secreting IL-10 (48). In *S. mansoni*-infected baboons downregulation of HG was temporally correlated with TGF-β production (97).

Regulatory cells appear in the spleen and HG when HG first appear. Thus, in vitro addition of SEA to HG cells from mice infected for 6 weeks with *S. mansoni* reduced IL-4, IL-5, and IL-10 production (78), and adding SEA to HG cells from mice infected for 8 weeks reduced IL-4 and IL-5 production (95). By adoptive transfer, SC that regulate HG formation were found 7 weeks postinfection (35). The appearance of regulatory cells as early as cellular and humoral immune responses (50) supports the recent provocative suggestion that generation of T_R cells may be an integral feature of the immune response (110).

In some studies it was not determined that the $CD8^+$ regulatory cells were T cells (129, 130). This is an important issue because in nonschistosomal systems $CD8^+$ non-T cells can induce or serve as regulatory cells. Thus, $CD8^+$ $CD11c^+$ lymphoid-derived DC cross-presented trinitrophenylated antigen to T_R cells, resulting in immunologic unresponsiveness (45). Plasmacytoid DC and other DC subsets rendered $CD4^+$ and $CD8^+$ T cells unresponsive and induced differentiation of native T cells into IL-10-producing T_R cells (80). Human $CD8^+$ T_R cells were generated by CD40-activated DC which produced IL-10 (53).

The role of $CD8^+$ DC in schistosomiasis is not clear. Schistosomal lysophosphatidylserine activated Toll-like receptor 2 (TLR2) and caused DC to induce the development of IL-10-producing T_R (136). However, 8 weeks after *S. mansoni* infection the numbers of splenic $CD8\alpha^+$ DC increased, and these cells were more activated with respect to MHC-II, C80, and CD40 than the cells in naïve mice (132). Then, depending on the nature of pathogen-derived signals and host-derived cytokines, these DC activated Th1 or Th2 cytokine responses. Therefore, $CD8^+$ DC might promote rather than inhibit immune responses in schistosomiasis. Thus, lymphocytes from patients chronically infected with *Schistosoma hematobium* showed reduced SEA-induced proliferation and cytokine production, but addition of DC isolated from these patients overcame this hyporesponsiveness (135). In this case TLR signaling might have enhanced T_E cell responses by overcoming $CD4^+$ $CD25^+$ T_R-cell suppression (108).

It is not known whether regulatory cells in schistosomiasis inhibit immune responses, including proliferative and cytokine responses and granuloma formation, directly by cell-cell contact (134) or indirectly by downregulating the activity of antigen-presenting cells (18, 137) and/or by production of immunoregulatory molecules, such as IL-4, IL-10, TGF-β, and prostaglandins (15, 30, 31, 32, 65, 97, 127, 149).

Multiple extrahepatic microenvironments. Adoptive transfer of $CD4^+$ and $CD8^+$ SC or LN cells from chronically infected mice to acutely infected mice downregulated HG formation. However, these regulatory cells might be activated and expanded in organs other than the spleen and LN, including mucosal tissues, and then homed into HG. Thus, when *S. mansoni* ova were injected into surgically fashioned cecal pouches of mice infected for 4 weeks, 4 weeks later these mice had significantly smaller HG than control mice that were not inoculated with ova or were inoculated with ova intraperito-

neally or subcutaneously (142). HG size was also reduced by adoptive transfer of splenocytes from mice which were infected for 8 weeks and which had received ova intracecally, but not intraperitoneally or subcutaneously, 4 weeks earlier. Suppression of HG was abolished when, before transfer, the cells were treated with antibodies to the T-cell markers Thy-1 and CD4, but not to CD8, and complement. These $CD4^+$ T cells inhibited in vitro migration of peritoneal exudate cells; i.e., they exhibited macrophage migration inhibitory activity (migration inhibitory factor) (141).

The TGF-β gene is expressed in HG (79), and TGF-β is produced by HG cells (13). In the baboon model SEA-induced elevated TGF-β production by peripheral blood mononuclear cells during chronic infection was correlated with diminished HG size, suggesting that this cytokine mediated HG downmodulation (97). Finally, TGF-β KO mice had larger PG than WT mice had (139).

Oral tolerance to a variety of antigens associated with development of T_R cells is generated by exposure of cells in the GALT to high concentrations of antigen that cross the epithelial cells from the lumen (140). Two subsets of T_R cells, Th3 and $CD4^+$ $CD25^+$, producing TGF-β and IL-10, respectively, were implicated in suppression of immune responses in infections with *Leishmania major* (8, 9), *Pneumocystis carinii* (61), and *Bordetella pertussis* (93) and in hepatitis C (89) and chronic retreoviral infections (63). In the last study the expression of surface CTLA-4 (CD152) appeared to be correlated with reduced blast cell formation. It is noteworthy that only in the study of *B. pertussis* (93) was it established that the T_R cells were pathogen specific. This is in contrast to evidence for $CD4^+$ SEA-specific T_R cells in schistosomiasis (141).

Role of apoptosis. Numerous large clusters of apoptotic cells appeared in the spleen and in inflammatory infiltrates around eggs in the liver 6 weeks after *S. mansoni* infection (40). Antibodies to IL-10 prevented TCR-induced T-cell apoptosis and enhanced TCR-stimulated secretion of Th1 cytokines. In another study 10 to 12 weeks postinfection 6% of splenic lymphocytes and 53.7% of HG lymphocytes were apoptotic (121). Apoptosis of splenic B cells and $CD4^+$ and $CD8^+$ T cells was observed during murine infection (88). Apoptosis of splenic $CD4^+$ T cells was significantly increased 6 weeks postinfection when egg laying was initiated in the liver. This apoptosis peaked at 8 weeks, decreased by 12 weeks, and then increased at 16 weeks. Almost 30% of HG $CD4^+$ T cells were apoptotic 8 and 16 weeks postinfection. SEA stimulated apoptosis of splenic and HG $CD4^+$ T helper lymphocytes prepared 6 to 16 weeks postinfection. This apoptosis was mediated by $FasL^+$ T and B cells, with FasL expression lowest before egg deposition (4 weeks), rising to a peak at 8 to 12 weeks (coincident with peak HG development), and then decreasing when HG were downregulated (16 weeks). Added SEA stimulated FasL expression by freshly isolated splenic B cells and $CD4^+$ and CD8+T lymphocytes from mice infected for at least 6 weeks. However, SEA did not enhance FasL expression by HG T or B lymphocytes. $CD4^+$ HG T lymphocytes from mice that were infected for 8 weeks exhibited significantly higher FasL expression than splenic $CD4^+$ T cells. Finally, SEA-stimulated lymphocytes induced lysis of Fas-bearing target cells. $CD4^+$ T-cell apoptosis was mediated by FasL-expressing $B\text{-}Ia^+$ cells (87).

These studies did not establish the significance of apoptosis with regard to regulation of granulomatous inflammation. Table 5 raises some questions that deal with this issue.

Role of retardation in development or destruction of ova. Viable miracidia in ova secrete SEA that trigger the DTH which initiates granuloma formation. Therefore, retardation of embryonation or accelerated destruction of ova should halt SEA secretion and, consequently, granuloma formation. The evidence for retardation of embyronation is sparse and unconvincing (51, 52). Egg destruction occurs in the course of schistosomiasis in mice (19) and rhesus monkeys (25). In vitro egg destruction by cytokine-activated eosinophils requiring SEA-specific antibody (66) has been observed, but its relevance to what happens in vivo is not clear. Moreover, in the mouse the extent of ovum destruction was not correlated with the downregulation of HG: the level of egg destruction was highest 7 weeks postinfection, when the inflammation was at its height, and was reduced when the inflammation had subsided 12 to 41 weeks postinfection (148). The relationship between the extent of egg destruction and granulomatous inflammation was not examined in infected rhesus monkeys (25).

Role of hormones of the hypothalamic-pituitary-adrenal axis. Serum levels of hypothalamic-pituitary-adrenal axis hormones, including corticotropin-releasing hormone, adrenocorticotropic hormone, dehydroepiandrosterone sulfate (DHEA-S), and cortisol, were assayed in *S. mansoni*-infected baboons for 12 weeks (98). During the primary infections the numbers of worms and eggs were high, and HG were large. As the infections progressed, the levels of these hormones, especially DHEA-S, decreased and the HG size decreased. In reexposed baboons the opposite pattern was observed: there were low numbers of worms and eggs, small HG, and hormone levels similar to or higher than the levels in uninfected baboons. Similar observations, including reduced levels of DHEA-S and cortisol, were made with primarily infected mice.

Further examination of the mechansims by which hormones of the hypothalamic-pituitary-adrenal axis regulate granulomatous inflammation should result in a deeper understanding of immune mechanisms. For instance, how are these mechanisms related to regulation of inflammation by T_R cells, macrophages, B cells, and FcγR and immunoregulatory molecules, including cytokines, chemokines, and prostaglandins?

DOWNREGULATION OF FIBROSIS

Experiments in which recombinant cytokines were injected (Table 3) implicated IL-7 in the downregulation of fibrosis (146). Studies of cytokine KO mice (Table 4) showed that B cells (47, 67) and Fcε-R-bearing cells (68) were involved in downregulation of this process. Daily intramuscular injections of IFN-γ for 4 weeks beginning 4 weeks postinfection decreased collagen deposition (39). This result contrasts with the inconsistent effects on fibrosis (1, 2, 154) of deletion of the IFN-γ and IFN-γ receptor genes (Table 4). The reasons for these discrepancies are not clear.

QUESTIONS FOR FURTHER STUDY

In this review I discuss a number of poorly understood or controversial observations and questions derived from these observations. Table 5 summarizes some of these observations

TABLE 5. Questions for further study

Subject	Key observations	Questions
Genetic control	Genetic control of HG formation and downregulation, fibrosis, epitope recognition, and Th1 and Th2 subset development	How are the processes genetically controlled? What genetic loci are involved?
Innate immunity	Schistosomal lyso-PS binds TLR2 on DC and induces IL-10-producing T_R cells[a]	Which schistosomal components bind TLR and induce innate immunity? Are TLRs and cells involved? What are the consequences for HG formation and downregulation?
Granuloma formation		
$CD4^+$ T cells	α/β, MHC-II dependent cells develop and expand and TCR diversify in extra hepatic microenvironments; many cells produce Th1 and Th2 cytokines coordinately but produce only low concentrations of IFN-γ; experiments with STAT4 and STAT6 KO mice concluded that Th2 cytokines, but not Th1 cytokines, are required for HG formation (done in infected mice also inoculated with ova)	Are microenvironments involved, and are GALT included? What are the roles of costimulatory, cytokine, chemokine, and receptor molecules in activation and expansion? What are the mechanisms of cell homing into granulomas? What molecular mechanisms account for coordinate Th1-Th2 cytokine production but low IFN-γ production by HG cells? What are the dynamics of TCR repertoire diversification in different microenvironments? What are the effects of STAT4 and STAT6 deletions in infected mice not inoculated with ova?
Other cells	Many other cell types are present in granulomas, including $CD8^+$ T cells, DC, eosinophils, mast cells, and fibrocytes	What are the contributions of these cells to expression of cytokines, chemokines, neuropeptides, and their receptors? What are the dynamics of expression versus granulomas?
Neuropeptides and receptors	Substance P receptor is involved in HG formation; other neuropeptides and receptors affect cytokine production and T-cell proliferation	What is more precise information about mechanisms of HG regulation by these molecules?
Fibrosis	Controlled by variety of molecules or cells; contradictory results (e.g., IFN-γ)	What are the roles and interactions among the molecules? What is the sequence or hierarchy of activity?
Downregulation of granulomatous inflammation	Apparent coordinate downregulation of granulomatous inflammation, T-cell expansion and expression of many molecules involved in T-cell activation, expansion, and homing; evidence for roles for T cells originating in extrahepatic compartments, HPA hormones, apoptosis of $CD4^+$ T cells mediated by $FasL^+$ la^+ B cells; B cells and FcγR required[b]	What are the roles of T_R cells, macrophages, DC, and other cells? What are the roles of immunomodulatory molecules and cell-cell contact? What is the pathogen specificity of the T_R cells? What are the mechanisms of hormonal involvement? What are the dynamics phenotypes, and interactions of different cell types (e.g., DC) in apoptosis and granuloma downregulation?
Balance between effector and regulatory T cells	In leishmaniasis balance between T_E and T_R cells appears to control parasite numbers in skin	Does a balance between SEA-reactive T_E and T_R cells control immunity, granuloma formation, and fibrosis in schistosomiasis?

[a] Lyso-PS, lyso-phosphatidylserine.
[b] HPA, hypothalmic-pituitary-adrenal.

and questions. Included are subjects which are in embryonic development (innate immunity); poorly understood (fibrosis, regulation by T cells, B cells, and FcγR, hormones, neuropeptides, chemokines); well developed at some levels but not at others (granuloma formation and downregulation); and speculation about how the balance between the parasite and the host is maintained.

SUMMARY

Many of the cellular and molecular elements required for development of granulomatous inflammation are present or appear soon after infection in extrahepatic tissues, such as mediastinal, mesenteric, and hepatic LN and spleens. Innate immune responses of different TLR to different schistosomal components might activate the function and/or expression of some of these elements, including antigen-presenting cells, costimulatory cytokine and chemokine molecules and their receptors, integrins on homing cells, and adhesion molecules on endothelial cells. Priming and expansion of the SEA-reactive $CD4^+$ T lymphocytes and the TCR diversification required for granuloma formation are stimulated by somular antigens that are cross-reactive with SEA. Presumably, distinct patterns of coordinate chemokine expression in the liver and draining LN determine which cell types are recruited into inflammatory sites initiated by the lodging of ova in the portal circulation and other microenvironments. HG formation and granuloma formation in other sites are initiated by SEA-specific, MHC-II-dependent, α/β^+ $CD4^+$ T-lymphocyte-induced DTH. Other SEA-reactive and nonreactive T cells and other cell types are present or are also recruited to the HG and presumably other granulomas. The other cells include $CD8^+$ T lymphocytes, B lymphocytes, activated eosinophils, mast cells, NK cells, basophils, macrophages, neutrophils, γ/δ^+ cells, non-B non-T cells, and fibrocytes.

HG formation is temporally correlated with the endogenous

SEA-induced production of both Th1 and Th2 cytokines in the spleen and HG. SEA epitope recognition and the development of Th1 or Th2 cytokine responses are under genetic control of the H-2 locus. The extent of HG inflammation is under non-H-2, multigene control. In response to high concentrations of endogenous SEA in the liver, there is terminal differentiation of $CD4^+$ T lymphocytes marked by cell cycle-independent cytokine gene expression (i.e., cytokine secretion by HG cells without appreciable lymphocyte proliferation). Many cells secrete IFN-γ, but at about 8 weeks postinfection HG cells produce very low concentrations of this cytokine.

Downmodulation of granulomatous inflammation, including its sequela, portal hypertension, is temporally associated with reduced expression of a variety of molecules involved in and/or required for activation, expansion, T- and B-lymphocyte antigen receptor diversification, induction of DTH, and, finally, homing of many cell types to form granulomas. Downregulation appears to be initiated in extrahepatic microenvironments, such as the spleen and perhaps the GALT. Downregulation requires B cells, FcγR, and possibly immune complexes reacting with these receptors to induce production of immunoregulatory molecules. It is not known whether downmodulation is mediated by cell-cell interactions and/or production or expression by T_R cells, macrophages, DC, and other cells with immunoregulatory molecules, such as IL-4, IL-10, TGF-β, CTLA-4, and prostaglandins. Downmodulation involves complex interactions among cytokines, chemokines, prostaglandins and their receptors, and other molecules, including CTLA-4, induced by reactions of schistosomal components and/or immune complexes with SEA-reactive T and B lymphocytes, TLR, and FcγR.

Eventually fibrosis appears in the granulomas. Fibrosis is under complex control by a number of cytokines produced by several cell types, but its regulation is clearly independent of regulation of granuloma formation.

The usual lack of serious deleterious effects on the host despite the presence of many adult worms and ova in the portal and intestinal circulation for months or years could depend upon the simultaneous appearance of and equilibrium in the liver and other tissues between SEA-specific T_E and T_R cells. Presumably, the T_E cells promote granuloma formation and protect the host against the deleterious effects of schistosomal products, and the T_R cells inhibit these T_E functions.

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REFERENCES

1. **Akhiani, A. A., N. Lycke, L. A. Nilsson, S. Olling, and O. Ouchterlony.** 1996. Lack of interferon-gamma receptor does not influence the outcome of infection in murine schistosomiasis mansoni. Scand. J. Immunol. **43:**257–262.
2. **Amiri, P., M. Haak-Frendscho, K. Robbins, J. H. McKerrow, T. Stewart, and P. Jardieu.** 1994. Anti-immunoglobulin E treatment decreases worm burden and egg production in *Schistosoma mansoni*-infected normal and interferon gamma knockout mice. J. Exp. Med. **180:**43–51.
3. **Amiri, P., R. M. Locksley, T. G. Parslow, M. Sadick, E. Rector, D. Ritter, and J. H. McKerrow.** 1992. Tumour necrosis factor alpha restores granulomas and induces parasite egg-laying in schistosome-infected SCID mice. Nature **356:**604–607.
4. **Amsden, A. F., and D. L. Boros.** 1979. Fc-receptor-bearing macrophages isolated from hypersensitivity and foreign-body granulomas. Delineation of macrophage dynamics, Fc receptor density/avidity and specificity. Am. J. Pathol. **96:**457–476.
5. **Angyalosi, G., V. Pancre, J. Herno, and C. Auriault.** 1998. Immunological response of major histocompatibility complex class II-deficient (Abeta(o)) mice infected by the parasite *Schistosoma mansoni*. Scand. J. Immunol. **48:**159–169.
6. **Asahi, H., H. J. Hernandez, and M. J. Stadecker.** 1999. A novel 62-kilodalton egg antigen from *Schistosoma mansoni* induces a potent $CD4^+$ T helper cell response in the C57BL/6 mouse. Infect. Immun. **67:**1729–1735.
7. **Asahi, H. O., A. Osman, R. M. Cook, P. T. LoVerde, and M. J. Stadecker.** 2000. *Schistosoma mansoni* phosphoenolpyruvate carboxykinase, a novel egg antigen: immunological properties of the recombinant protein and identification of a T-cell epitope. Infect. Immun. **68:**3385–3393.
8. **Aseffa, A., A. Gumy, P. Launois, H. R. MacDonald, J. A. Louis, and F. Tacchini-Cottier.** 2002. The early IL-4 response to *Leishmania major* and the resulting Th2 cell maturation steering progressive disease in BALB/c mice are subject to the control of regulatory $CD4^+$ $CD25^+$ T cells. J. Immunol. **169:**3232–3241.
9. **Belkaid, Y., C. A. Piccirillo, S. Mendez, E. M. Shevach, and D. L. Sacks.** 2002. $CD4^+$ $CD25^+$ regulatory T cells control *Leishmania major* persistence and immunity. Nature **420:**502–507.
10. **Berger, S., H. Ballo, and H. J. Stutte.** 1996. Distinct antigen-induced cytokine pattern upon stimulation with antibody-complexed antigen consistent with a Th1 →Th2-shift. Res. Virol. **147:**103–108.
11. **Blum, A. M., A. Metwali, M. Kim-Miller, J. Li, K. Qadir, D. E. Elliott, B. Lu, Z. Fabry, N. Gerard, and J. V. Weinstock.** 1999. The substance P receptor is necessary for a normal granulomatous response in murine schistosomiasis mansoni. J. Immunol. **162:**6080–6085.
12. **Blum, A. M., A. Metwali, R. C. Mathew, G. Cook, D. Elliott, and J. V. Weinstock.** 1992. Granuloma T lymphocytes in murine schistosomiasis mansoni have somatostatin receptors and respond to somatostatin with decreased IFN-gamma secretion. J. Immunol. **149:**3621–3626.
13. **Boros, D. L.** 1994. The role of cytokines in the formation of the schistosome egg granuloma. Immunobiology **191:**441–450.
14. **Boros, D. L., A. F. Amsden, and A. T. Hood.** 1982. Modulation of granulomatous hypersensitivity. IV. Immunoglobulin and antibody production by vigorous and immunomodulated liver granulomas of *Schistosoma mansoni*-infected mice. J. Immunol. **128:**1050–1053.
15. **Boros, D. L., and J. R. Whitfield.** 1998. Endogenous IL-10 regulates IFN-gamma and IL-5 cytokine production and the granulomatous response in *Schistosomiasis mansoni*-infected mice. Immunology **94:**481–487.
16. **Boros, D. L., and J. R. Whitfield.** 1999. Enhanced Th1 and dampened Th2 responses synergize to inhibit acute granulomatous and fibrotic responses in murine schistosomiasis mansoni. Infect. Immun. **67:**1187–1193.
17. **Cai, Y., J. G. Langley, D. I. Smith, and D. L. Boros.** 1996. A cloned major *Schistosoma mansoni* egg antigen with homologies to small heat shock proteins elicits Th1 responsiveness. Infect. Immun. **64:**1750–1755.
18. **Cederbom, L., H. Hall, and F. Ivars.** 2000. $CD4^+$ $CD25^+$ regulatory T cells down-regulate co-stimulatory molecules on antigen-presenting cells. Eur. J. Immunol. **30:**1538–1543.
19. **Cheever, A. W., and L. A. Anderson.** 1971. Rate of destruction of *Schistosoma mansoni* eggs in the tissues of mice. Am. J. Trop. Med. Hyg. **20:**62–68.
20. **Cheever, A. W., R. H. Duvall, and T. A. J. Hallack.** 1984. Differences in hepatic fibrosis and granuloma size in several strains of mice infected with *Schistosoma japonicum*. Am. J. Trop. Med. Hyg. **33:**602–607.
21. **Cheever, A. W., R. H. Duvall, T. A. J. Hallack, R. G. Minker, J. D. Malley, and K. G. Malley.** 1987. Variation of hepatic fibrosis and granuloma size among mouse strains infected with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. **37:**85–97.
22. **Cheever, A. W., F. D. Finkelman, P. Caspar, S. Heiny, J. G. Macedonia, and A. Sher.** 1992. Treatment with anti-IL-2 antibodies reduces hepatic pathology and eosinophilia in *Schistosoma mansoni*-infected mice while selectively inhibiting T cell IL-5 production. J. Immunol. **148:**3244–3248.
23. **Cheever, A. W., F. D. Finkelman, and T. M. Cox.** 1995. Anti-interleukin-4 treatment diminishes secretion of Th2 cytokines and inhibits hepatic fibrosis in murine schistosomiasis japonica. Parasite Immunol. **17:**103–109.
24. **Cheever, A. W., R. W. Poindexter, and T. A. Wynn.** 1999. Egg laying is delayed but worm fecundity is normal in SCID mice infected with *Schistosoma japonicum* and *S. mansoni* with or without recombinant tumor necrosis factor alpha treatment. Infect. Immun. **67:**2201–2208.
25. **Cheever, A. W., and K. G. Powers.** 1971. Rate of destruction of *Schistosoma mansoni* eggs and adult worms in the tissues of rhesus monkeys. Am. J. Trop. Med. Hyg. **20:**69–76.
26. **Cheever, A. W., M. E. Williams, T. A. Wynn, F. D. Finkelman, R. A. Seder, T. M. Cox, S. Hieny, P. Caspar, and A. Sher.** 1994. Anti-IL-4 treatment of *Schistosoma mansoni*-infected mice inhibits development of T cells and

non-B, non-T cells expressing Th2 cytokines while decreasing egg-induced hepatic fibrosis. J. Immunol. **153:**753–759.
27. **Cheever, A. W., Y. Xu, A. Sher, F. D. Finkelman, T. M. Cox, and J. G. Macedonia.** 1993. *Schistosoma japonicum*-infected mice show reduced hepatic fibrosis and eosinophilia and selective inhibition of interleukin-5 secretion by $CD4^+$ cells after treatment with anti-interleukin-2 antibodies. Infect. Immun. **61:**1288–1292.
28. **Cheever, A. W., Y. H. Xu, A. Sher, and J. G. Macedonia.** 1991. Analysis of egg granuloma formation in *Schistosoma japonicum*-infected mice treated with antibodies to interleukin-5 and gamma interferon. Infect. Immun. **59:**4071–4074.
29. **Chensue, S. W., D. L. Boros, and C. S. David.** 1980. Regulation of granulomatous inflammation in murine schistosomiasis. In vitro characterization of T lymphocyte subsets involved in the production and suppression of migration inhibition factor. J. Exp. Med. **151:**1398–1412.
30. **Chensue, S. W., S. L. Kunkel, G. I. Higashi, P. A. Ward, and D. L. Boros.** 1983. Production of superoxide anion, prostaglandins, and hydroxyeicosatetraenoic acids by macrophages from hypersensitivity-type (*Schistosoma mansoni* egg) and foreign body-type granulomas. Infect. Immun. **42:**1116–1125.
31. **Chensue, S. W., S. L. Kunkel, P. A. Ward, and G. I. Higashi.** 1983. Exogenously administered prostaglandins modulate pulmonary granulomas induced by *Schistosoma mansoni* eggs. Am. J. Pathol. **111:**78–87.
32. **Chensue, S. W., D. G. Remick, G. I. Higashi, D. L. Boros, and S. L. Kunkel.** 1986. Modulation of murine schistosomiasis by exogenously administered prostaglandins. Am. J. Pathol. **125:**28–34.
33. **Chensue, S. W., K. S. Warmington, N. W. Lukacs, P. M. Lincoln, M. D. Burdick, R. M. Strieter, and S. L. Kunkel.** 1995. Monocyte chemotactic protein expression during schistosome egg granuloma formation. Sequence of production, localization, contribution, and regulation. Am. J. Pathol. **146:**130–138.
34. **Chesney, J., C. Metz, A. B. Stavitsky, M. Bacher, and R. Bucala.** 1998. Regulated production of type I collagen and inflammatory cytokines by peripheral blood fibrocytes. J. Immunol. **160:**419–425.
35. **Colley, D. G.** 1976. Adoptive suppression of granuloma formation. J. Exp. Med. **143:**696–700.
36. **Colley, D. G., N. Katz, R. S. Rocha, W. Abrantes, A. L. da Silva, and G. Gazzinelli.** 1983. Immune responses during human schistosomiasis mansoni. IX. T-lymphocyte subset analysis by monoclonal antibodies in hepatosplenic disease. Scand. J. Immunol. **17:**297–302.
37. **Cook, G. A., A. Metwali, A. Blum, R. Mathew, and J. V. Weinstock.** 1993. Lymphokine expression in granulomas of *Schistosoma mansoni*-infected mice. Cell. Immunol. **152:**49–58.
38. **Crabtree, J. E., C. E. Pullar, L. K. Trejdosiewicz, and R. A. Wilson.** 1992. Murine intestinal humoral responses in chronic *Schistosoma mansoni* infections. Scand. J. Immunol. **35:**361–367.
39. **Czaja, M. J., F. R. Weiner, S. Takahashi, M. A. Giambrone, P. H. van der Meide, H. Schellekens, L. Biempica, and M. A. Zern.** 1989. Gamma-interferon treatment inhibits collagen deposition in murine schistosomiasis. Hepatology **10:**795–800.
40. **Estaquier, J., M. Marguerite, F. Sahuc, N. Bessis, C. Auriault, and J. C. Ameisen.** 1997. Interleukin-10-mediated T cell apoptosis during the T helper type 2 cytokine response in murine *Schistosoma mansoni* parasite infection. Eur. Cytokine Netw. **8:**153–160.
41. **Falcone, F. H., C. A. Dahinden, B. F. Gibbs, T. Noll, U. Amon, H. Hebestreit, O. Abrahamsen, J. Klaucke, M. Schlaak, and H. Haas.** 1996. *Schistosoma mansoni* egg antigen. Eur. J. Immunol. **26:**1147–1155.
42. **Fallon, P. G., and D. W. Dunne.** 1999. Tolerization of mice to *Schistosoma mansoni* egg antigens causes elevated type 1 and diminished type 2 cytokine responses and increased mortality in acute infection. J. Immunol. **162:**4122–4132.
43. **Fanning, M. M., P. A. Peters, R. S. Davis, J. W. Kazura, and A. A. Mahmoud.** 1981. Immunopathology of murine infection with *Schistosoma mansoni*: relationship of genetic background to hepatosplenic disease and modulation. J. Infect. Dis. **144:**148–153.
44. **Farah, I. O., M. Nyindo, M. A. Suleman, J. Nyaundi, T. M. Kariuki, R. E. Blanton, L. H. Elson, and C. L. King.** 1997. *Schistosoma mansoni*: development and modulation of the granuloma after or multiple exposures in the baboon (*Papio cynocephalus anubis*). Exp. Parasitol. **86:**93–101.
45. **Ferguson, T. A., J. Herndon, B. Elzey, T. S. Griffith, S. Schoenberger, and D. R. Green.** 2002. Uptake of apoptotic antigen-coupled cells by lymphoid dendritic cells and cross-priming of $CD8^+$ T cells produce active immune unresponsiveness. J. Immunol 2002. **168:**5589–5595.
46. **Fernandez, N., M. Renedo, C. Garcia-Rodriguez, and C. M. Sanchez.** 2002. Activation of monocytic cells through Fc gamma receptors induces the expression of macrophage-inflammatory protein (MIP)-1α, MIP-1β, and RANTES. J. Immunol. **169:**3321–3328.
47. **Ferru, I., O. Roye, M. Delacre, C. Auriault, and I. Wolowczuk.** 1998. Infection of B-cell-deficient mice by the parasite *Schistosoma mansoni*: demonstration of the participation of B cells in granuloma modulation. Scand. J. Immunol. **48:**233–240.
48. **Flores, V. P., T. S. Harris, D. E. Ricklan, and M. J. Stadecker.** 1994. Macrophages from schistosomal egg granulomas induce unresponsiveness in specific cloned Th-1 lymphocytes in vitro and down-regulate schistosomal granulomatous disease in vivo. J. Immunol. **152:**1847–1855.
49. **Flores-Villanueva, P. O., X. X. Zheng, T. B. Strom, and M. J. Stadecker.** 1996. Recombinant IL-10 and IL-10/Fc treatment down-regulate egg antigen-specific delayed hypersensitivity reactions and egg granuloma formation in schistosomiasis. J. Immunol. **156:**3315–3320.
50. **Garb, K. S., A. B. Stavitsky, and A. A. Mahmoud.** 1981. Dynamics of antigen and mitogen-induced responses in murine schistosomiasis japonica: in vitro comparison between hepatic granulomas and splenic cells. J. Immunol. **127:**115–120.
51. **Garcia, E. G., G. F. Mitchell, J. M. Beall, and W. U. Tiu.** 1985. *Schistosoma japonicum*: the modulation of lung granuloma and inhibition of egg maturation in mice by human sera. Asian Pac. J. Allergy Immunol. **3:**156–160.
52. **Garcia, E. G., G. F. Mitchell, F. P. Tapales, and W. U. Tiu.** 1983. Reduced embryonation of *Schistosoma japonicum* eggs as a contributory mechanism in modulation of granuloma in chronically sensitized mice. Southeast Asian J. Trop. Med. Public Health **14:**272–273.
53. **Gilliet, M., and Y. J. Liu.** 2002. Generation of human CD8 T regulatory cells by CD40 ligand-activated plasmacytoid dendritic cells. J. Exp. Med. **195:**695–704.
54. **Greenfield, E. A., K. A. Nguyen, and V. K. Kuchroo.** 1998. CD28/B7 costimulation: a review. Crit. Rev. Immunol. **18:**389–418.
55. **Grzych, J. M., E. Pearce, A. Cheever, Z. A. Caulada, P. Caspar, S. Heiny, F. Lewis, and A. Sher.** 1991. Egg deposition is the major stimulus for the production of Th2 cytokines in murine schistosomiasis mansoni. J. Immunol. **146:**1322–1327.
56. **Hernandez, H. J., C. M. Edson, D. A. Harn, C. J. Ianelli, and M. J. Stadecker.** 1998. *Schistosoma mansoni*: genetic restriction and cytokine profile of the $CD4^+$ T helper cell response to dominant epitope peptide of major egg antigen Sm-p40. Exp. Parasitol. **90:**122–130.
57. **Hernandez, H. J., A. H. Sharpe, and M. J. Stadecker.** 1999. Experimental murine schistosomiasis in the absence of B7 costimulatory molecules: reversal of elicited T cell cytokine profile and partial inhibition of egg granuloma formation. J. Immunol. **162:**2884–2889.
58. **Hernandez, H. J., Y. Wang, and M. J. Stadecker.** 1997. In infection with *Schistosoma mansoni*, B cells are required for T helper type 2 cell responses but not for granuloma formation. J. Immunol. **158:**4832–4837.
59. **Hogan, L. H., M. Wang, M. Suresh, D. O. Co, J. V. Weinstock, and M. Sandor.** 2002. $CD4^+$ TCR repertoire heterogeneity in *Schistosoma mansoni*-induced granulomas. J. Immunol. **169:**6386–6393.
60. **Hood, A. T., and D. L. Boros.** 1980. The effect of splenectomy on the pathophysiology and egg-specific immune response of *Schistosoma mansoni*-infected mice. Am. J. Trop. Med. Hyg. **29:**586–591.
61. **Hori, S., T. L. Carvalho, and J. Demengeot.** 2002. $CD25^+$ $CD4^+$ regulatory T cells suppress $CD4^+$ T cell-mediated pulmonary hyperinflammation driven by *Pneumocystis carinii* in immunodeficient mice. Eur. J. Immunol. **32:**1282–1291.
62. **Iacomini, J., D. E. Ricklan, and M. J. Stadecker.** 1995. T cells expressing the gamma delta T cell receptor are not required for egg granuloma formation in schistosomiasis. Eur. J. Immunol. **25:**884–888.
63. **Iwashiro, M., R. J. Messer, K. E. Peterson, I. M. Stromnes, T. Sugie, and K. J. Hasenkrug.** 2001. Immunosuppression by $CD4^+$ regulatory T cells induced by chronic retroviral infection. Proc. Natl. Acad. Sci. **98:**9226–9230.
64. **Jacobs, W., J. Bogers, A. Deelder, M. Wery, and E. Van Marck.** 1997. Adult *Schistosoma mansoni* worms positively modulate soluble egg antigen-induced inflammatory hepatic granuloma formation in vivo. Stereological analysis and immunophenotyping of extracellular matrix proteins, adhesion molecules, and chemokines. Am. J. Pathol. **150:**2033–2045.
65. **Jacobs, W., S. Kumar-Singh, J. Bogers, K. Van de Vijver, A. Deelder, and E. Van Marck.** 1998. Transforming growth factor-beta, basement membrane components and heparan sulphate proteoglycans in experimental hepatic schistosomiasis mansoni. Cell Tissue Res. **292:**101–106.
66. **James, S. L., and D. G. Colley.** 1978. Eosinophil-mediated destruction of *Schistosoma mansoni* eggs in vitro. II. The role of cytophilic antibody. Cell. Immunol. **38:**35–47.
67. **Jankovic, D., A. W. Cheever, M. C. Kullberg, T. A. Wynn, G. Yap, P. Caspar, F. A. Lewis, R. Clynes, J. V. Ravetch, and A. Sher.** 1998. $CD4^+$ T cell-mediated granulomatous pathology in schistosomiasis is downregulated by a B cell-dependent mechanism requiring Fc receptor signaling. J. Exp. Med. **187:**619–629.
68. **Jankovic, D., M. C. Kullberg, D. Dombrowicz, S. Barbieri, P. Caspar, T. A. Wynn, W. E. Paul, A. W. Cheever, J. P. Kinet, and A. Sher.** 1997. Fc epsilonRI-deficient mice infected with *Schistosoma mansoni* mount normal Th2-type responses while displaying enhanced liver pathology. J. Immunol. **159:**1868–1875.
69. **Jankovic, D., M. C. Kullberg, N. Noben-Trauth, P. Caspar, W. E. Paul, and A. Sher.** 2000. Single cell analysis reveals that IL-4 receptor/Stat6 signaling is not required for the in vivo or in vitro development of $CD4^+$ lymphocytes with a Th2 cytokine profile. J. Immunol. **164:**3047–3055.
70. **Jankovic, D., M. C. Kullberg, N. Noben-Trauth, P. Caspar, J. M. Ward, A. W. Cheever, W. E. Paul, and A. Sher.** 1999. Schistosome-infected IL-4

receptor knockout (KO) mice, in contrast to IL-4 KO mice, fail to develop granulomatous pathology while maintaining the same lymphokine expression profile. J. Immunol. **163:**337–342.
71. **Joseph, A. L., and D. L. Boros.** 1993. Tumor necrosis factor plays a role in *Schistosoma mansoni* egg-induced granulomatous inflammation. J. Immunol. **151:**5461–5471.
72. **Kaplan, C. D., S. K. O'Neill, T. Koreny, M. Czipri, and A. Finnegan.** 2002. Development of inflammation in proteoglycan-induced arthritis is dependent on Fc gammaR regulation of the cytokine/chemokine environment. J. Immunol. **169:**5851–5859.
73. **Kaplan, M. H., J. R. Whitfield, D. L. Boros, and M. J. Grusby.** 1998. Th2 cells are required for the *Schistosoma mansoni* egg-induced granulomatous response. J. Immunol. **160:**1850–1856.
74. **Kee, K. C., D. W. Taylor, J. S. Cordingley, A. E. Butterworth, and A. J. Munro.** 1986. Genetic influence on the antibody response to antigens of *Schistosoma mansoni* in chronically infected mice. Parasite Immunol. **8:**565–574.
75. **Khoury, P. B., S. S. Lloyd, W. A. Reid, D. J. Weiner, S. M. Phillips, and E. J. Soulsby.** 1981. Kinetics and characterization of antigen-binding and antibody-producing cells in the regional draining lymph nodes and spleen during initial murine schistosomiasis. I. Cellular responses against cercarial immunogens. Cell. Immunol. **59:**233–245.
76. **Khoury, P. B., and S. M. Phillips.** 1981. Kinetics and characterization of antigen-binding and antibody-producing cells in the regional draining lymph nodes and spleen during initial murine schistosomiasis. II. Cellular responses against egg immunogens. Cell. Immunol. **59:**246–255.
77. **King, C. L., J. Xianli, I. Malhotra, S. Liu, A. A. Mahmoud, and H. C. Oettgen.** 1997. Mice with a targeted deletion of the IgE gene have increased worm burdens and reduced granulomatous inflammation following primary infection with *Schistosoma mansoni*. J. Immunol. **158:**294–300.
78. **King, C. L., Jia, Xianli, and A. B. Stavitsky.** 2001. Murine schistosomiasis mansoni: coordinate cytokine regulation and differences in cellular immune responses of granuloma cells and splenocytes to endogenous and exogenous schistosome egg antigens. Parasite Immunol. **23:**607–615.
79. **Kresina, T. F., Q. He, E. S. Degli, and M. A. Zern.** 1994. Gene expression of transforming growth factor beta 1 and extracellular matrix proteins in murine *Schistosoma mansoni* infection. Gastroenterology **107:**773–780.
80. **Kuwana, M.** 2002. Induction of anergic and regulatory T cells by plasmacytoid dendritic cells and other dendritic cell subsets. Hum. Immunol. **63:**1156–1163.
81. **La Flamme, A. C., A. S. MacDonald, C. R. Huxtable, M. Carroll, and E. J. Pearce.** 2003. Lack of C3 affects Th2 response development and the sequelae of chemotherapy in schistosomiasis. J. Immunol. **170:**470–476.
82. **Langley, J. G., and D. L. Boros.** 1995. T-lymphocyte responsiveness in murine schistosomiasis mansoni is dependent upon the adhesion molecules intercellular adhesion molecule-1, lymphocyte function-associated antigen-1, and very late antigen-4. Infect. Immun. **63:**3980–3986.
83. **Lawley, T. J., E. A. Ottesen, R. A. Hiatt, and L. A. Gazze.** 1979. Circulating immune complexes in acute schistosomiasis. Clin. Exp. Immunol. **37:**221–227.
84. **Leptak, C. L., and J. H. McKerrow.** 1997. Schistosome egg granulomas and hepatic expression of TNF-alpha are dependent on immune priming during parasite maturation. J. Immunol. **158:**301–307.
85. **Lukacs, N. W., and D. L. Boros.** 1991. Identification of larval cross-reactive and egg-specific antigens involved in granuloma formation in murine schistosomiasis mansoni. Infect. Immun. **59:**3237–3242.
86. **Lukacs, N. W., and D. L. Boros.** 1993. Lymphokine regulation of granuloma formation in murine schistosomiasis mansoni. Clin. Immunol. Immunopathol. **68:**57–63.
87. **Lundy, S. K., and D. L. Boros.** 2002. Fas ligand-expressing B-1a lymphocytes mediate $CD4^+$-T-cell apoptosis during schistosomal infection: induction by interleukin 4 (IL-4) and IL-10. Infect. Immun. **70:**812–819.
88. **Lundy, S. K., S. P. Lerman, and D. L. Boros.** 2001. Soluble egg antigen-stimulated T helper lymphocyte apoptosis and evidence for cell death mediated by $FasL^+$ T and B cells during murine *Schistosoma mansoni* infection. Infect. Immun. **69:**271–280.
89. **MacDonald, A. S., M. I. Araujo, and E. J. Pearce.** 2002. Immunology of parasitic helminth infections. Infect. Immun. **70:**427–433.
90. **Mathew, R. C., and D. L. Boros.** 1986. Anti-L3T4 antibody treatment suppresses hepatic granuloma formation and abrogates antigen-induced interleukin-2 production in *Schistosoma mansoni* infection. Infect. Immun. **54:**820–826.
91. **Mathew, R. C., S. Ragheb, and D. L. Boros.** 1990. Recombinant IL-2 therapy reverses diminished granulomatous responsiveness in anti-L3T4-treated, *Schistosoma mansoni*-infected mice. J. Immunol. **144:**4356–4361.
92. **McAdam, A. J., T. T. Chang, A. E. Lumelsky, E. A. Greenfield, V. A. Boussiotis, J. S. Duke-Cohan, T. Chernova, N. Malenkovich, C. Jabs, V. K. Kuchroo, V. Ling, M. Collins, A. H. Sharpe, and G. J. Freeman.** 2000. Mouse inducible costimulatory molecule (ICOS) expression is enhanced by CD28 costimulation and regulates differentiation of $CD4^+$ T cells. J. Immunol. **165:**5035–5040.
93. **McGuirk, P., C. McCann, and K. H. Mills.** 2002. Pathogen-specific T regulatory 1 cells induced in the respiratory tract by a bacterial molecule that stimulates interleukin 10 production by dendritic cells: a novel strategy for evasion of protective T helper type 1 responses by *Bordetella pertussis*. J. Exp. Med. **195:**221–231.
94. **Metwali, A., A. Blum, D. E. Elliott, and J. V. Weinstock.** 2002. Interleukin-4 receptor alpha chain and STAT6 signaling inhibit gamma interferon but not Th2 cytokine expression within schistosome granulomas. Infect. Immun. **70:**5651–5658.
95. **Metwali, A., D. Elliott, A. M. Blum, J. Li, M. Sandor, R. Lynch, N. Noben-Trauth, and J. V. Weinstock.** 1996. The granulomatous response in murine schistosomiasis mansoni does not switch to Th1 in IL-4-deficient C57BL/6 mice. J. Immunol. **157:**4546–4553.
96. **Metwali, A., D. Elliott, R. Mathew, A. Blum, and J. V. Weinstock.** 1993. IL-2 contributes to the IL-5 response in granulomas from mice infected with *Schistosoma mansoni*. J. Immunol. **150:**536–542.
97. **Mola, P. W., I. O. Farah, T. M. Kariuki, M. Nyindo, R. E. Blanton, and C. L. King.** 1999. Cytokine control of the granulomatous response in *Schistosoma mansoni*-infected baboons: role of exposure and treatment. Infect. Immun. **67:**6565–6571.
98. **Morales-Montor, J., E. Newhouse, F. Mohamed, A. Baghdadi, and R. T. Damian.** 2001. Altered levels of hypothalamic-pituitary-adrenocortical axis hormones in baboons and mice during the course of infection with *Schistosoma mansoni*. J. Infect. Dis. **183:**313–320.
99. **Mosmann, T. R., and R. L. Coffman.** 1989. Heterogeneity of cytokine secretion patterns and functions of helper T cells. Adv. Immunol. **46:**111–147.
100. **Mosmann, T. R., L. Li, and S. Sad.** 1997. Functions of CD8 T-cell subsets secreting different cytokine patterns. Semin. Immunol. **9:**87–92.
101. **Mountford, A. P., S. Anderson, and R. A. Wilson.** 1996. Induction of Th1 cell-mediated protective immunity to *Schistosoma mansoni* by co-administration of larval antigens and IL-12 as an adjuvant. J. Immunol. **156:**4739–4745.
102. **Olds, G. R., S. el Meneza, A. F. Mahmoud, and T. F. Kresina.** 1989. Differential immunoregulation of granulomatous inflammation, portal hypertension, and hepatic fibrosis in murine schistosomiasis mansoni. J. Immunol. **142:**3605–3611.
103. **Olds, G. R., and A. B. Stavitsky.** 1986. Mechanisms of in vivo modulation of granulomatous inflammation in murine schistosomiasis japonicum. Infect. Immun. **52:**513–518.
104. **Oliveira, V. R., M. C. el-Cheikh, A. M. Aguiar, A. Balduino, B. de Fatima, L. F. Reis, and R. Borojevic.** 2000. *Schistosoma mansoni* egg-induced hepatic granulomas in mice deficient for the interferon-gamma receptor have altered populations of macrophages, lymphocytes and connective tissue cells. Microbes Infect. **2:**1817–1826.
105. **Owhashi, M., Y. Horii, T. Ikeda, H. Maruyama, T. Abe, and Y. Nawa.** 1990. Importance of mast-cell-derived eosinophil chemotactic factor A on granuloma formation in murine schistosomiasis japonica: evaluation using mast-cell-deficient W/WV mice. Int. Arch. Allergy Appl. Immunol. **92:**64–68.
106. **Owhashi, M., Y. Nawa, and N. Watanabe.** 1989. Granulomatous response in selective IgE-deficient SJA/9 mice infected with *Schistosoma japonicum*. Int. Arch. Allergy Appl. Immunol. **90:**310–312.
107. **Park, M. K., K. F. Hoffmann, A. W. Cheever, D. Amichay, T. A. Wynn, and J. M. Farber.** 2001. Patterns of chemokine expression in models of *Schistosoma mansoni* inflammation and infection reveal relationships between type 1 and type 2 responses and chemokines in vivo. Infect. Immun. **69:**6755–6768.
108. **Pasare, C., and R. Medzhitov.** 2003. Toll pathway-dependent blockade of $CD4^+$ $CD25^+$ T cell-mediated suppression by dendritic cells. Science **299:**1033–1036.
109. **Pedras-Vasconcelos, J. A., and E. J. Pearce.** 1996. Type 1 $CD8^+$ T cell responses during infection with the helminth *Schistosoma mansoni*. J. Immunol. **157:**3046–3053.
110. **Powrie, F., and K. J. Maloy.** 2003. Immunology: regulating the regulators. Science **299:**1030–1031.
111. **Qiu, B., K. A. Frait, F. Reich, E. Komuniecki, and S. W. Chensue.** 2001. Chemokine expression dynamics in mycobacterial (type-1) and schistosomal (type-2) antigen-elicited pulmonary granuloma formation. Am. J. Pathol. **158:**1503–1515.
112. **Ragheb, S., and D. L. Boros.** 1989. Characterization of granuloma T lymphocyte function from *Schistosoma mansoni*-infected mice. J. Immunol. **142:**3239–3246.
113. **Rathore, A., C. Sacristan, D. E. Ricklan, V. P. Flores, and M. J. Stadecker.** 1996. In situ analysis of B7–2 costimulatory, major histocompatibility complex class II, and adhesion molecule expression in schistosomal egg granulomas. Am. J. Pathol. **149:**187–194.
114. **Ravetch, J. V., and R. A. Clynes.** 1998. Divergent roles for Fc receptors and complement in vivo. Annu. Rev. Immunol **16:**421–432.
115. **Raziuddin, S., S. Shetty, and A. Ibrahim.** 1992. Phenotype, activation and lymphokine secretion by gamma/delta T lymphocytes from schistosomiasis and carcinoma of the urinary bladder. Eur. J. Immunol. **22:**309–314.
116. **Rengarajan, J., S. J. Szabo, and L. H. Glimcher.** 2000. Transcriptional regulation of Th1/Th2 polarization. Immunol. Today **21:**479–483.

117. **Rezende, S. A., K. J. Gollob, R. Correa-Oliveira, and A. M. Goes.** 1998. Down modulation of MHC surface molecules on B cells by suppressive immune complexes obtained from chronic intestinal schistosomiasis patients. Immunol. Lett. **62:**67–73.
118. **Rezende, S. A., V. R. Oliveira, A. M. Silva, J. B. Alves, A. M. Goes, and L. F. Reis.** 1997. Mice lacking the gamma interferon receptor have an impaired granulomatous reaction to *Schistosoma mansoni* infection. Infect. Immun. **65:**3457–3461.
119. **Rezende, S. A., D. N. Silva-Teixeira, S. C. Drummond, and A. M. Goes.** 1997. IL-10 plays a role in the modulation of human granulomatous hypersensitivity against *Schistosoma mansoni* eggs induced by immune complexes. Scand. J. Immunol. **46:**96–102.
120. **Rumbley, C. A., H. Sugaya, S. A. Zekavat, M. El Refaei, P. J. Perrin, and S. M. Phillips.** 1999. Activated eosinophils are the major source of Th2-associated cytokines in the schistosome granuloma. J. Immunol. **162:**1003–1009.
121. **Rumbley, C. A., S. A. Zekavat, H. Sugaya, P. J. Perrin, M. A. Ramadan, and S. M. Phillips.** 1998. The schistosome granuloma: characterization of lymphocyte migration, activation, and cytokine production. J. Immunol. **161:**4129–4137.
122. **Rutitzky, L. I., E. Ozkaynak, J. B. Rottman, and M. J. Stadecker.** 2003. Disruption of the ICOS-B7RP-1 costimulatory pathway leads to enhanced hepatic immunopathology and increased gamma interferon production by CD4 T cells in murine schistosomiasis. Infect. Immun. **71:**4040–4044.
123. **Sabin, E. A., and E. J. Pearce.** 1995. Early IL-4 production by non-$CD4^+$ cells at the site of antigen deposition predicts the development of a T helper 2 cell response to *Schistosoma mansoni* eggs. J. Immunol. **155:**4844–4853.
124. **Shang, X. Z., B. C. Chiu, V. Stolberg, N. W. Lukacs, S. L. Kunkel, H. S. Murphy, and S. W. Chensue.** 2002. Eosinophil recruitment in type-2 hypersensitivity pulmonary granulomas: source and contribution of monocyte chemotactic protein-3 (CCL7). Am. J. Pathol. **161:**257–266.
125. **Sher, A., R. L. Coffman, S. Hieny, P. Scott, and A. W. Cheever.** 1990. Interleukin 5 is required for the blood and tissue eosinophilia but not granuloma formation induced by infection with *Schistosoma mansoni*. Proc. Natl. Acad. Sci. **87:**61–65.
126. **Sher, A., D. Fiorentino, P. Caspar, E. Pearce, and T. Mosmann.** 1991. Production of IL-10 by $CD4^+$ T lymphocytes correlates with down-regulation of Th1 cytokine synthesis in helminth infection. J. Immunol. **147:**2713–2716.
127. **Stadecker, M. J., J. K. Kamisato, and S. M. Chikunguwo.** 1990. Induction of T helper cell unresponsiveness to antigen by macrophages from schistosomal egg granulomas. A basis for immunomodulation in schistosomiasis? J. Immunol. **145:**2697–2700.
128. **Stavitsky, A. B., and K. S. Garb.** 1984. Spontaneous and egg antigen-induced syntheses of immunoglobulin and antibody by spleen cells and hepatic granulomas of mice infected with *Schistosoma japonicum*. Infect. Immun. **46:**276–278.
129. **Stavitsky, A. B., and W. W. Harold.** 1988. Deficiency of interleukin-2 activity upon addition of soluble egg antigen to cultures of spleen cells from mice infected with *Schistosoma japonicum*. Infect. Immun. **56:**1778–1784.
130. **Stavitsky, A. B., and W. W. Harold.** 1989. Deficiency of interleukin-2 production upon addition of soluble egg antigen to cultures of isolated hepatic granulomas or hepatic granuloma cells from mice infected with *Schistosoma japonicum*. Infect. Immun. **57:**2339–2344.
131. **Stavitsky, A. B., G. R. Olds, and L. B. Peterson.** 1985. Regulation of egg antigen-induced in vitro proliferative response by splenic suppressor T cells in murine *Schistosoma japonicum* infection. Infect. Immun. **49:**635–640.
132. **Straw, A. D., A. S. MacDonald, E. Y. Denkers, and E. J. Pearce.** 2003. CD154 plays a central role in regulating dendritic cell activation during infections that induce Th1 or th2 responses. J. Immunol. **170:**727–734.
133. **Subramanian, G., J. W. Kazura, E. Pearlman, X. Jia, I. Malhotra, and C. L. King.** 1997. B7–2 requirement for helminth-induced granuloma formation and CD4 type 2 T helper cell cytokine expression. J. Immunol. **158:**5914–5920.
134. **Takahashi, Y., P. R. Dutta, D. M. Cerasoli, and G. Kelsoe.** 1998. In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. V. Affinity maturation develops in two stages of clonal selection. J. Exp. Med. **187:**885–895.
135. **van Den Biggelaar, A. H., J. L. Grogan, Y. Filie, R. Jordens, P. G. Kremsner, F. Koning, and M. Yazdanbakhsh.** 2000. Chronic schistosomiasis: dendritic cells generated from patients can overcome antigen-specific T cell hyporesponsiveness. J Infect. Dis. **182:**260–265.
136. **van der Kleij, D., E. Latz, J. F. Brouwers, Y. C. Kruize, M. Schmitz, E. A. Kurt-Jones, T. Espevik, E. C. de Jong, M. L. Kapsenberg, D. T. Golenbock, A. G. Tielens, and M. Yazdanbakhsh.** 2002. A novel host-parasite lipid cross-talk. Schistosomal lyso-phosphatidylserine activates toll-like receptor 2 and affects immune polarization. J. Biol. Chem. **277:**48122–48129.
137. **Vendetti, S., J. G. Chai, J. Dyson, E. Simpson, G. Lombardi, and R. Lechler.** 2000. Anergic T cells inhibit the antigen-presenting function of dendritic cells. J. Immunol. **165:**1175–1181.
138. **Virgin, H. W., G. F. Wittenberg, and E. R. Unanue.** 1985. Immune complex effects on murine macrophages. I. Immune complexes suppress interferon-gamma induction of Ia expression. J. Immunol. **135:**3735–3743.
139. **Wahl, S. M., M. Frazier-Jessen, W. W. Jin, J. B. Kopp, A. Sher, and A. W. Cheever.** 1997. Cytokine regulation of schistosome-induced granuloma and fibrosis. Kidney Int. **51:**1370–1375.
140. **Weiner, H. L.** 2001. Oral tolerance: immune mechanisms and the generation of Th3-type TGF-beta-secreting regulatory cells. Microbes Infect. **3:**947–954.
141. **Weinstock, J. V.** 1987. Immunoregulation of granulomatous inflammation in the liver and intestines, p. 151–175. *In* M. N. Marsh (ed.), Immunopathology of the small intestine. John Wiley and Sons Ltd., New York, N.Y.
142. **Weinstock, J. V., A. M. Blum, and J. T. Kassab.** 1985. Induction of granuloma modulation in murine schistosomiasis mansoni by enteric exposure to schistosome eggs. J. Immunol. **135:**560–563.
143. **Weinstock, J. V., and D. L. Boros.** 1981. Heterogeneity of the granulomatous response in the liver, colon, ileum, and ileal Peyer's patches to schistosome eggs in murine schistosomiasis mansoni. J. Immunol. **127:**1906–1909.
144. **Weinstock, J. V., and D. L. Boros.** 1982. Alteration of granuloma angiotensin I-converting enzyme activity by regulatory T lymphocytes in murine schistosomiasis. Infect. Immun. **35:**465–470.
145. **Weinstock, J. V., S. W. Chensue, and D. L. Boros.** 1983. Modulation of granulomatous hypersensitivity. V. Participation of histamine receptor positive and negative lymphocytes in the granulomatous response of *Schistosoma mansoni*-infected mice. J. Immunol. **130:**423–427.
146. **Wolowczuk, I., M. Delacre, O. Roye, S. L. Giannini, and C. Auriault.** 1997. Interleukin-7 in the skin of *Schistosoma mansoni*-infected mice is associated with a decrease in interferon-gamma production and leads to an aggravation of the disease. Immunology **91:**35–44.
147. **Wyler, D. J.** 1996. Fibrosin, a novel fibrogenic protein: discovery, cloning and implications for fibrotic disorders. Int. Arch. Allergy Immunol. **111:**326–329.
148. **Wyler, D. J., S. M. Wahl, A. W. Cheever, and L. M. Wahl.** 1981. Fibroblast stimulation in schistosomiasis. I. Stimulation in vitro of fibroblasts by soluble products of egg granulomas. J. Infect. Dis. **144:**254–262.
149. **Wynn, T. A., A. W. Cheever, M. E. Williams, S. Hieny, P. Caspar, R. Kuhn, W. Muller, and A. Sher.** 1998. IL-10 regulates liver pathology in acute murine schistosomiasis mansoni but is not required for immune down-modulation of chronic disease. J. Immunol. **160:**4473–4480.
150. **Wynn, T. A., I. P. Oswald, I. A. Eltoum, P. Caspar, C. J. Lowenstein, F. A. Lewis, S. L. James, and A. Sher.** 1994. Elevated expression of Th1 cytokines and nitric oxide synthase in the lungs of vaccinated mice after challenge infection with *Schistosoma mansoni*. J. Immunol. **153:**5200–5209.
151. **Xu, Y. H., J. Macedonia, A. Sher, E. Pearce, and A. W. Cheever.** 1991. Dynamic analysis of splenic Th1 and Th2 lymphocyte functions in mice infected with *Schistosoma japonicum*. Infect. Immun. **59:**2934–2940.
152. **Yamashita, T., and D. L. Boros.** 1990. Changing patterns of lymphocyte proliferation, IL-2 production and utilization, and IL-2 receptor expression in mice infected with *Schistosoma mansoni*. J. Immunol. **145:**724–731.
153. **Yamashita, T., and D. L. Boros.** 1992. IL-4 influences IL-2 production and granulomatous inflammation in murine schistosomiasis mansoni. J. Immunol. **149:**3659–3664.
154. **Yap, G., A. Cheever, P. Caspar, D. Jankovic, and A. Sher.** 1997. Unimpaired down-modulation of the hepatic granulomatous response in CD8 T-cell- and gamma interferon-deficient mice chronically infected with *Schistosoma mansoni*. Infect. Immun. **65:**2583–2586.

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