

PATHOGENESIS OF *SCHISTOSOMA MANSONI* INFECTION

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In this paper a discussion is made on the pathogenesis of schistosomiasis mansoni in mice, presented from the perspectives of "processes", "mediators", "strategies for study" and "disease". These concepts overlap considerably. Regarding "processes", granulomas, fibrosis and vasculitis are discussed. The role of mediators, including cells, antibodies and immune complexes, cytokines and distal mediators is commented as related to the pathological processes occurring in schistosomiasis.

Finally, strategies for study are presented, followed by a discussion on the etiopathogenesis of the different clinical stages and pathologic manifestations of schistosomiasis mansoni.

Key words: schistosomiasis – *Schistosoma mansoni* – mice – pathogenesis

Schistosoma mansoni worms develop to maturity in the host over a period of 5 weeks, at which time egg laying begins. Eggs in the tissues require 1 week to mature and the miracidium then survives for 3 weeks. After death of the miracidium the granulomas involute, decrease in size and change from a mixture of eosinophils, and mononuclear cells to a fibrotic lesion.

During the first 5 weeks of infection T-helper 1 (Th1) cells are dominant in the murine immune response with gamma interferon (IFN- γ) and interleukin-2 (IL-2) responses dominant. After egg laying begins, Th2-type responses dominate the immune response (Sher et al., 1990) and secretion of IL-4, IL-5 and IL-10 is prominent (Sher et al., 1991). IL-4 secretion is associated with IgE production and eosinophilia is dependent upon IL-5. IL-10 down-regulates the Th1 response.

As the infection continues, at about the 12th week, immunological down-regulation occurs (Mathew et al., 1990). *In vitro* cell-proliferation to soluble egg antigen (SEA) decreases, granulomas around recently laid eggs are smaller and the rate of collagen synthesis in the liver decreases (Olds et al., 1989).

My discussion of pathogenesis will be presented from the perspectives of "processes", "mediators", "strategies for study" and "disease". These concepts overlap considerably.

PROCESSES

Granulomas – (1) Formation of granulomas is a function of cellular immunity mediated by CD4⁺ T cells. There is disagreement as to whether Th1 or Th2 type cells are most important (Cheever et al., 1991; Boros & Lukacs, 1991). (2) Immunologic down-regulation of immune responses is regulated by CD4⁺ "helper-suppressor" T cells and CD8⁺ "effector-suppressor" T cells (Perrin & Phillips, 1989; Mathew et al., 1990). as well as by α -idiotypic antibodies (Montesano et al., 1990).

Fibrosis – (1) Fibrosis is a dynamic process with variations in the rates of synthesis, destruction and degree of cross-linking of collagen (Grimaud & Lortat-Jacob, 1991). (2) The various isotypes of collagen are regulated differently during the course of infection (Olds et al., 1989).

Vasculitis – (1) Vasculitis induced by granulomas, classically in the lung and liver. (2) Vasculitis mediated by immune complexes.

MEDIATORS

Cells – (1) CD4⁺ and CD8⁺ T cells are key for the induction and regulation of granuloma formation. (2) Dendritic cells, macrophages and lymphocytes may present antigens. Antigen presentation may influence the type of cell response which predominates. (3) Inflammatory cells.

Antibodies and immune complexes – (1) These are not important for the formation of granulomas (Cheever et al., 1985). (2) Antibodies, with the exception of anti-idiotypic antibodies, have little role in the regulation of granuloma size but may regulate fibrosis to some extent (Olds et al., 1989). (3) Immune complexes appear to be important in acute-toxic schistosomiasis.

Cytokines – (1) Cytokines are secreted by a wide variety of cells and have complex effects on nearly all cell types. (2) The probable role of cytokines has been examined by measuring cytokines (or their mRNAs) in cells from infected animals, by injection of α -cytokine antibodies or by administration of cytokines to infected animals.

α -IL-5 antibodies prevent accumulation of eosinophils but have little effect on granuloma size or fibrosis (Sher et al., 1990). α -IL-4 antibodies prevent IgE formation and a marked effect or no effect on granuloma formation has been found by different investigators (Boros & Lukacs, 1991; Cheever et al., 1991). α -IFN- γ has no evident effect on granulomas in the mouse liver (Sher et al., 1990) but large doses of exogenous IFN- γ decrease granuloma size and fibrosis (Czaja et al., 1989a). IL-2 has variously been reported to be prominent (Mathew et al., 1990) or absent (Sher et al., 1990; Henderson et al., 1991) in murine schistosomiasis mansoni. α -IL-2 antibodies decrease granuloma size slightly and fibrosis strikingly (Cheever et al., 1991). Exogenous IL-2 restores the size of modulated granulomas in chronically infected or CD4⁺ depleted mice (Perrin & Phillips, 1989; Mathew et al., 1990). Transforming growth factor beta (TGF- β) is prominent in infected mouse livers (Czaja, 1989b). IL-1 and tumor necrosis factor (TNF) have not been extensively studied but one would predict that they should be important and Chensue et al. (1989) found sequential production of IL-1 and TNF in macrophages from pulmonary granulomas around injected eggs. A new cytokine, fibroblast stimulating factor-1 (Prakash et al., 1991), has been reported from CD4⁺ cells of *S. mansoni* infected mice (Wyller & Prakash, 1991).

Distal mediators – Little is known of the role of more distal mediators in the inflammatory process such as phospholipase A₂, histamine, arachidonic acid metabolites, lysophosphatides, reactive oxygen species etc. (Weinstock, 1991).

STRATEGIES FOR STUDY

Longitudinal study of infected hosts – Granuloma size, fibrosis and other pathologic features change during the course of infection and this may be related to concomitant changes in parasitologic findings, mediators and other aspects of the immune response. Ultrasonographic diagnosis of portal fibrosis (Abdel Wahab, 1991) adds an important dimension to longitudinal studies in man.

Passive administration of immune serum, monoclonal antibodies or cells – In addition to their more obvious utility these techniques allow the study of granulomas of a similar age, e.g. an 8 week infection in mice, in an immunologically modified environment. Injection of eggs into the lungs or the production of granulomas *in vitro* gives the investigator even more defined conditions, although these are increasingly remote from conditions in the infected host.

Injection of blocking agents – (1) Antibodies against B cells, T cells, eosinophils etc. have been used. (2) Chemical blockade, e.g. with prostaglandin inhibitors. (3) Antibodies against cytokines.

Injection of mediators – IFN- γ , IL-2 and IL-4 have been the principal mediators examined to date.

Examination of deficient animals – Mice deficient in complement, mast cells, T cells (nude) and T and B cells (severe combined immunodeficiency, SCID) have been examined with and without partial reconstitution of deficiencies. Nutritional deficiencies have been extensively studied in mice and humans (Coutinho, 1991). Transgenic mice with selective “knockout” of IL-2, IL-4 or other genes will provide excellent models.

DISEASE

Acute toxic schistosomiasis – (1) Antigen-antibody complexes seem important in acute disease and intensity of infection is related to the severity of symptoms (Hiatt et al., 1979) although individuals with low intensity of infection may develop severe disease. (2) Lack of immune regulation is part of the acute syndrome and the symptoms improve as the host develops regulatory mechanisms. The passage of antigens or α -SEA antibodies from

mother to fetus, inducing development of α -idiotypic antibodies, may protect against acute disease (Eloi-Santos et al., 1989). (3) Better definition of acute disease in humans and experimental models (Damian, 1991) is vital to our understanding of this syndrome.

Indeterminate (intestinal) or asymptomatic schistosomiasis – Low intensity of infection and effective modulation by t cells or α -idiotypic antibodies are important variables.

Chronic disease – (Nash, 1982; Andrade, 1991) – (1) The development of *hepatosplenic disease* is influenced by the intensity of infection, the duration of infection, lack of effective immune regulation (Montesano et al., 1990) and the genetic makeup of the host (Prata, 1991). Portal hypertension is caused by intrahepatic portal vascular obstruction. Liver function is relatively well preserved but the anatomic expansion of the arterial circulation, a possible explanation for this, seems not to be functionally important (Paranaguá-Vezozo & Cerri, 1991). *Glomerulonephritis* occurs mostly in patients with hepatosplenic disease and the shunting of immune complexes around the liver is presumably an important reason for this. *Cardiopulmonary schistosomiasis* similarly depends on the shunting of eggs from the portal system to the pulmonary arterial circulation where obstruction by granulomatus pulmonary arteritis produces pulmonary hypertension. (2) *Symptomatic intestinal disease* with diarrhea and colic is uncommonly reported from controlled studies in Brazil, except for patients with acute toxemic disease, but is increasingly reported from Africa (Gryseels & Polderman, 1991). Colonic polyposis with severe cholera-like diarrhea is even more limited in its distribution. The pathogenesis of these lesions and symptoms is not understood, or much studied, in infected persons nor have experimental models been defined. (3) *Bilharziomas*, localized inflammatory masses containing numerous eggs are frequently located in or near the intestines. Nothing is known of the factors that lead the worms to remain in a local area to produce such lesions although models are available in animals infected with *S. japonicum* and *S. haematobium*.

Ectopic lesions – (1) Ectopic lesions may occur in acute or chronic infections and seem unrelated to intensity of infection. Lesions in the skin and central nervous system are most frequently reported. These are generally asso-

ciated with the presence of egg-laying adult worms at the ectopic site although some lesions of the spinal cord are attributed to vasospasm. The reason for ectopic localization of worms is unknown and I am unaware of experimental models.

Associated diseases – These are beyond the scope of the present presentation but much is known of the association of salmonella with schistosomes and the apparent association of hepatitis B and schistosomal hepatic fibrosis is the subject of continuing investigation and controversy (Chieffi, 1991).

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