American Journal of Pathology, Vol. 142, No. 3, March 1993

Commentary

Schistosomiasis

Infection versus Disease and Hypersensitivity versus Immunity

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Schistosomiasis is one of the major infectious diseases affecting developing countries. Infection is contracted by exposure to fresh water containing helminth cercariae shed by infected snails. Cercariae penetrate the skin, migrate intravascularly to the liver, and later lay eggs in the mesenteric (*Schistosoma mansoni* and *Schistosoma japonicum*) or urogenital (*Schistosoma haematobium*) venules. About 200 million persons are infected with schistosomes but probably <5% of these have clinically important schistosomal disease. Thus, it is vital to distinguish infected persons from individuals who actually have the disease. Estimation of the intensity of infection is also key.

The number of worms (worm burden) carried by each infected individual is relatively constant, because schistosomes do not multiply in the vertebrate host. Infection intensity may be increased by repeated exposure or decreased through attrition of senescent worms, through host immunity, or after chemotherapy. The intensity of infection in different individuals is extremely variable and those heavily infected are most likely to develop disease,[1–3] and heavy infection may be a necessary but not sufficient condition for the development of pipestem fibrosis.[1] Unfortunately, lightly infected mice cannot be studied since 1 pair of worms in an animal this size constitutes an infection more intense than that in almost all infected persons.[2] However, immune responses are also important determinants of disease.

Schistosomal Disease and Pipestem Fibrosis

The pathognomonic periportal fibrosis (clay pipestem fibrosis or Symmers' fibrosis) associated with the syndrome of hepatosplenic schistosomiasis is one of the most common causes of portal hypertension worldwide. Ultrasound is now the method of choice for the diagnosis of Symmers' fibrosis and has been used in the field to evaluate regression of fibrosis after treatment.[4]

Hepatic pathology in schistosomiasis is secondary to an immunologically mediated reaction to the eggs. Infected persons who develop Symmers' fibrosis lack regulatory idiotypes present in individuals without Symmers' fibrosis.[5] The report by Henderson et al[6] in this issue of the Journal reproduces in a murine model the association between pipestem fibrosis and the absence of T cell-stimulatory idiotypes. This model opens the way to clarification of the immunopathogenesis of this important lesion.

Experimental pipestem fibrosis has been described in chimpanzees infected with *S. mansoni*[7] or *S. japonicum*[8] and in rabbits infected with *S. japonicum*.[9] Reports of pipestem fibrosis in *S. mansoni*-infected mice[10,11] were not entirely convincing. In my own material I was concerned by the lack of diffuse portal fibrosis and by livers showing atrophy in some lobes and hyperplasia in others. The report by Henderson et al[6] is completely convincing.

In all of these models it has been speculated that changes in the intrahepatic circulation shunt eggs into the portal tracts, feeding an increasing proportion of eggs into portal areas once portal fibrosis is

Accepted for publication October 26, 1992.

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initiated.[1,7–9,11] In chimpanzees and rabbits[7–9] significant portal fibrosis occurred early in infection, when eggs still lay mainly outside portal tracts. In *S. mansoni*-infected humans portal accumulation of eggs was demonstrated only when portal fibrosis was present.[1] Thus, in its initial stage pipestem fibrosis may be an early event not caused by the fusion of fibrotic granulomas. The portal accumulation of eggs found uniformly in humans with pipestem fibrosis and in all experimental models occurs at a later stage.

Host Immune Response to Eggs

The circumoval granuloma and the associated fibrosis are basic to the immunopathogenesis of schistosomiasis even if their relation to the initiation of portal fibrosis is unclear. Hypersensitivity to schistosome eggs is generally measured as the size of granulomas in the livers of infected animals or in the lungs of animals given intravenous injections of eggs. In infected humans the response of peripheral blood mononuclear cells to soluble antigen or the size of granulomas formed *in vitro* by these cells is used. $CD4^+$ T helper (Th) cells are central in these responses.[12] Th1 cells are associated with classical delayed hypersensitivity and with secretion of interferon-γ and interleukin (IL)-2.[13] Th2 cells are associated with hyperergic responses and secrete IL-4, important for IgE responses, and IL-5, necessary for the development of eosinophils.

S. mansoni eggs lead to an augmented Th2 response and down-regulation of the Th1 response in infected mice,[14] but there is controversy as to the importance of Th1 and Th2 responses in the pathogenesis of the granuloma and of hepatic fibrosis. It is clear that the development of granulomas in mice is accompanied by a complex orchestration of cytokine responses in which IL-2 and IL-4 are both important.[12,15–17] A Th1 cell line responding to egg antigen accelerated the granulomatous response to injected schistosome eggs,[18] but the participation of eosinophils suggests rapid recruitment of Th2 cells. Perhaps Th1 cells or another sources of IL-2 are important for the initial response to *S. mansoni* eggs.

Abundant transforming growth factor-β, associated with fibrosis in other systems,[19] is demonstrable in the livers of *S. mansoni*-infected mice.[20] Treatment of mice with large doses of interferon-γ inhibits granuloma formation and fibrosis,[21] although treatment with anti-interferon-γ has no effect.[16,22] Anti-IL-5 treatment prevents the accumulation of eosinophils in the granulomas but surprisingly has virtually no effect on granuloma size or hepatic fibrosis.[22] A newly described cytokine, fibroblast-stimulating factor, is seen in the livers of *S. mansoni*-infected mice.[23]

Striking results were reported by Amiri et al,[24] who partially restored granulomas in severe combined immunodeficient mice by injecting TNF-α. Presumably, formation of local circumoval lesions in the absence of antigen recognition requires chemotactic factors from the eggs to direct cells activated by tumor necrosis factor. Weinstock[25] has reviewed the effects of kinins, angiotensin, and neuropeptides on the formation and regulation of schistosomal granulomas.

Immunological down-regulation of the size of granulomas around newly laid eggs occurs during schistosome infection. Granulomas diminish in size gradually after the 8th week of *S. mansoni* infection and rapidly after the 7th week of *S. japonicum* infection in mice. The mechanism of down-regulation in *S. mansoni*-infected mice is predominantly cellular,[12,15] and much evidence implicates $CD8^+$ cells, although induction of unresponsiveness in $CD4^+$ cells has also been postulated.[26] In *S. japonicum* infections modulation is mediated largely through antibodies, including anti-idiotypic antibodies.[27] The regulation of hepatic fibrosis is frequently dissociated from regulation of granuloma size in both *S. mansoni* and *S. japonicum* infections,[27,28] as is the case in the mice described in this issue by Henderson et al.[6]

Immunity And Antischistosome Vaccines

Prevention and control of schistosomal disease is generally based on reduction of the worm burden, generally through chemotherapy.[29] In the future, infection intensity might be more efficiently reduced by vaccination, and the vaccine need not be 100% effective to achieve disease control. Resistance to reinfection with schistosomes has been frequently documented experimentally. Some resistance is clearly related to nonspecific factors affecting the migration of developing schistosomes (schistosomules). However, extensive studies of specific immunity have been made after immunization with irradiation-attenuated cercariae[30–32] or with purified or recombinant antigens or after administration of monoclonal antibodies.[33] Resistance is almost always only partial. A staggering number of effector systems exist.[33] The Th1 response, particularly interferon-γ and activated macrophages, is often important in mice vaccinated a single time with irradiation-attenuated cercariae[30,34] but after repeated vaccination the Th2 response is prominent and immunity can be passively transferred with serum.[30] In rats Th2

responses involving eosinophils (or macrophages or platelets) and IgE are often important.[33] In many instances *in vivo* evidence supports *in vitro* data concerning cytotoxicity of these mechanisms. A recent pair of papers confirm earlier evidence that schistosomules are disposed of in the lungs of mice by being extruded live from the capillaries into the alveolar spaces.[31,32] If this mechanism is widely used to eliminate schistosomules, then these observations need to be reconciled with the apparent killing of schistosomules by cytotoxic antibodies and cells.

The decreasing prevalence and intensity of infection in older children and adults suggested immunity to reinfection in humans, but careful documentation of the degree of exposure in putatively immune and nonimmune individuals was required because patterns of water contact change markedly with age. Immunity was found to develop slowly in children after years of infection. Less resistant children infected with *S. mansoni* had higher titers of antibodies that blocked immune effector function than did more resistant children.[35] Eosinophils and IgE antibodies appear to be important for resistance to *S. mansoni* and *S. haematobium*.[33,36]

Contemporary biology offers new tools that are particularly welcome for studying organisms that are antigenically complex and adapted for prolonged survival in the mammalian host. Schistosome infections provide excellent opportunities for examining chronic inflammation, immunoregulation, and the functions of eosinophils and IgE. Recombinant antigens may be useful for vaccine development but a breakthrough in vaccination will likely require better understanding of immunity as well as new antigens and adjuvants. Unfortunately, we are not likely to experience a shortage of infected humans to study for some time; but the model described here[6] will certainly generate new directions for the study of pipestem fibrosis.

Acknowledgments

I am grateful to Theodore Nash, Alan Sher, Thomas Wynn, Robert Bergquist, and Isam Eltoum for helpful discussions.

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