Chapter 9

IMMUNOPATHOLOGY IN EXPERIMENTAL SCHISTOSOMIASIS

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1. PATHOGENESIS

In Schistosomiasis mansoni, parasites migrate to the mesenteric veins where they begin laying hundreds of eggs per day approximately 4 to 5 weeks post-infection. Some eggs are trapped in the microvasculature of the liver where they induce a vigorous granulomatous response. Subsequently, in severe cases fibrosis and portal hypertension develop. These are the primary causes of morbidity in infected individuals and may eventually be lethal due to variceal bleeding. Consequently, much of the symptomatology of schistosomiasis is attributed to the egg-induced granulomatous response and the associated pathology. Although the magnitude and location of pathology differs with other schistosome species, the pathogenic mechanisms are likely similar. Therefore, given the wealth of information on the immunopathology of S. mansoni infection, we have restricted our discussion to recent progress in this area.

As mentioned above hepatic granulomas are pathogenic because they precipitate fibrosis, which obstructs blood flow, increases portal blood pressure, and ultimately promotes development of portal-systemic venous shunts. CD4+ Th cells are essential for granuloma formation, while all other lymphocytes examined so far (including B cells, CD8+ T cells, NK T cells, and γδ T cells) do not appear to be involved, at least in the early initiation
phases of granuloma development (1). Studies aimed at dissecting the respective roles of type-1- (IFN-γ, IL-2, TNF-α) and type-2 CD4+ T cell-associated cytokines (IL-4, IL-5, IL-6, IL-9, IL-13) in granuloma formation showed that the granulomatous response evolves from an early type-1 to a sustained and dominant type-2 cytokine response (2). The importance of CD4+ Th2 cells to the pathogenesis of schistosomiasis was shown in experiments in which mice vaccinated with egg antigen extracts plus IL-12 to induce an egg-specific CD4+ Th1 response upon subsequent infection, developed smaller granulomas and less severe fibrosis than did non-vaccinated Th2-polarized controls (3-6). Decreased fibrosis was associated with a diminished type-2 response and increased type-1 cytokine production.

Although granulomas are detrimental because they eventually “scar” the liver, it is clear that the egg-induced lesions also serve an important host-protective function, particularly in S. mansoni infections. During infection, antigens secreted by schistosome eggs provide a continuous and potent stimulus for the immune response. If these antigens are not sequestered or neutralized effectively, they may trigger a persistent and tissue damaging host immune response. In support of this conclusion, CD4+ T-cell-deprived, egg-tolerized, and some IL-4− and IL-10− mice die earlier than comparably infected, immunologically intact control mice because they are unable to satisfactorily mount a normal type-2-dominant response (7). Widespread microvesicular hepatic damage induced by toxic egg products contributed to the death of the infected mice, particularly in the case of nude and SCID mice (8). Presumably, the detrimental effect of chronic type-2 cytokine expression (e.g. fibrosis and portal hypertension) represents a compromise solution for the parasite and host as the parasite can persist only when the host survives. Because of the central role played by type-2 cytokines, much work on the pathogenesis of schistosomiasis is focused on the mechanisms that initiate, maintain, and suppress type-2 immunity.

2. THE GENERATION OF TYPE-2 RESPONSES

Type-2-defective Stat6, IL-4R, and IL-4/IL-13-deficient mice are all severely impaired in granuloma formation and fibrosis while type-1-defective Stat1- (unpublished observation), Stat4-, IFN-γ-, and IL-12p40-deficient mice show only minor changes in pathology (9-11), confirming the critical role of type-2 cytokines in disease progression. Surprisingly, while the mechanisms that initiate type-1 immunity have been described in detail in a variety of models (12), the mechanisms that promote type-2 responses are much less clear. Many studies suggested that accessory cells such as mast cells, basophils, Kupffer cells, eosinophils, or non-B, non-T cells