Granulomatous Response in Selective IgE-Deficient SJA/9 Mice Infected with *Schistosoma japonicum*

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Abstract

Granulomatous response was examined in selective IgE-deficient SJA/9 mice infected with *Schistosoma japonicum*. The average size of granulomas formed around newly deposited eggs in SJA/9 mice was significantly smaller than that in control C57BL/6 or SJL/J mice, although the numbers of adult worms recovered from each strain were comparable among them. Thus, IgE antibody specific to allergenic components of *S. japonicum* eggs seems to act as an amplifier for the formation of granulomatous lesions.

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Soluble egg antigen (SEA) of *Schistosoma japonicum* contains at least two major allergenic components of glycoprotein nature [1,2]. Immediate hyper-sensitivity response against SEA is observed in *S. japonicum*-infected mice in parallel with the development of granulomatous lesions in the liver [3]. Furthermore, a high titer of specific IgE antibody against SEA can be detected in the sera of infected mice and humans [4]. However, the actual role of specific IgE antibody in the pathogenesis of granuloma formation around deposited eggs remains obscure. In the present study, therefore, the relative importance of IgE antibody was evaluated by using SJA/9 mice. This strain is selectively deficient in IgE production [5, 6] due to a genetic defect in collaboration between T cells and precursor IgE B cells [7].

Six SJA/9 (H-2S), seven SJL/J (H-2S), and six C57BL/6 (H-2b) mice were infected by intraperitoneal injection with 30 cercariae of *S. japonicum* (Japanese strain). All mice used were males and 12–14 weeks old at the time of infection. They were sacrificed at 8 weeks postinfection by exsanguination through the inferior vena cava while under ether anesthesia. Sera from each strain of mice were separately pooled and their IgE antibody titers against SEA of *S. japonicum* were measured by passive cutaneous anaphylaxis (PCA) reaction in the dorsal skin of Wistar rats by the method of Watanabe and Ovary [8] with slight modification [1]. SEA was prepared as described previously [1]. The dose of SEA used as a challenge antigen for PCA was determined by preliminary experiments. For histological examination of granulomatous lesions, a piece of liver was removed from each mouse immediately after sacrifice, fixed in buffered formalin, dehydrated in an ascending series of ethanol, and embedded in paraffin wax. Tissues were sectioned at 6- μ m thickness and stained with hematoxylin-eosin. Diameter of granulomas around newly deposited eggs was measured under a microscope and the mean area calculated according to the method described by Colley [9]. Worm burden of each mouse was determined by a method described previously [4].

Results are summarized in figure 1. The size of granuloma formed around newly deposited eggs in SJA/9 mice was significantly ($p < 0.01$) smaller than that in C57BL/6 or SJL/J mice (fig. 1A). When PCA titer of the pooled serum from each strain against SEA was examined, C57BL/6 and SJL/J mice were good responders, whereas SJA/9 mice were completely unresponsive (fig. 1B). Numbers of *S.japonicum* adult worms recovered from each strain were comparable (8.0 ± 2.8 from C57BL/6, 5.7 ± 2.6 from SJL/J, and 7.3 ± 3.5 from SJA/9) and the difference among them was statistically not significant ($p > 0.1$).

Granulomatous lesions observed in *S.japonicum* infection are much more severe than those in *Schistosoma mansoni* or *Schistosoma haematobium* infection because of higher output of eggs by *S.japonicum* adult worms [10, 11]. Immediate-type hypersensitivity

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Fig. 1. Mean granuloma size around newly deposited eggs in the liver (A) and specific IgE antibody levels measured by PCA (B) of three strains of mice infected with *S.japonicum*. Groups of C57BL/6, SJL/J, and SJA/9 mice were infected with 30 cercariae of *S.japonicum*. Histological specimens and sera were obtained 8 weeks after infection. Vertical bar represents SE of the mean.

response to SEA has been assumed to be a major effector mechanism for the granuloma formation in schistosomiasis japonica [3]. However, recently Cheever et al. [12, 13] emphasized the possible importance of T-cell-mediated immunity on granuloma formation. In the present study, although the size was significantly smaller, granulomatous lesions were formed around newly deposited eggs in the liver of SJA/9 mice. Delayed hypersensitivity reaction in SJA/9 mice is reported to be comparable to that in SJL/J mice [14]. As to the mechanisms of granuloma formation, various mechanisms other than immediate hypersensitivity reaction should be considered. For example, *S.japonicum* eggs per se have eosinophil chemotactic factors [15, 16]. Furthermore, granuloma T cells produce eosinophilotactic lymphokine [17,18]. Thus, IgE antibody specific to SEA is not a prerequisite for the granuloma formation, but rather acts as an amplifier of the granuloma formation in schistosomiasis japonica. Although mast cells are rare in peri-ovular granulomas [19], mast cell-derived eosinophil chemotactic factor of anaphylaxis (ECF-A) is detectable in the systemic circulation of *S.japonicum*-infected mice [20] and ECF-A is known to enhance the chemotactic reactivity of

eosinophils to SEA [21]. Such a mechanism seems to be defective in SJA/9 mice because of their defect in IgE production.

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