Eosinophils, but Not Eosinophil Peroxidase or Major Basic Protein, Are Important for Host Protection in Experimental Brugia pahangi Infection

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The attenuation of eosinophilia by the administration of monoclonal antibodies to CCR3 consistently correlates with impairment in worm elimination following primary intraperitoneal Brugia pahangi infections in mice. Host protection was unimpaired in mice deficient in eosinophil peroxidase (EPO) or major basic protein 1 (MBP-1), suggesting that eosinophils are essential in host protection but that neither EPO nor MBP-1 alone is.

Despite the consistent association of eosinophilia with parasitic infections, evidence supporting a host-protective role in vivo remains elusive (1-4, 16, 22). The function of eosinophils has been studied by modulating their numbers by manipulating interleukin-5 levels (5) (13) or depleting them selectively with a monoclonal antibody against the eotaxin receptor CCR3 (8). Eosinophilia correlates with improved host protection in Angiostrongylus cantonensis (19), Strongyloides ratti (17), Strongyloides stercoralis (12), Onchocerca volvulus (14), and Lito- mosoides sigmodontis (15) infections. In contrast, the depletion of eosinophils did not alter the course of Schistosoma mansoni (20), Mesocostoides corti (13), and Trichuris muris (3) infections. In the case of filarial parasites, eotaxin and eosinophils (20), Mesocestoides corti (19), and Brugia pahangi (17) infections. In contrast, the depletion of eosinophils did not alter the course of Schistosoma mansoni (20), Mesocostoides corti (13), and Trichuris muris (3) infections. In the case of filarial parasites, eotaxin and eosinophils have been shown to play a role in host protection (21).

The role of eosinophil granule constituents in host protection is also unclear. Purified eosinophil granule proteins have been shown to effectively kill Brugia microfilariae (11), schis- tosomulae (2), and Trichinella spiralis newborn larvae (10) in vitro. Gutierrez-Pena et al. (9) have shown that the death of onchocercal microfilariae following amoxicillin treatment was associated with eosinophil degranulation. Electron microscopy analyses showed apposition of eosinophil granule material on the microfilarial surface. However, the requirement of eosinophil granule protein for in vivo host protection has not been studied extensively. In a recent study, EPO−/− and wild-type (WT) mice challenged with O. volvulus manifested similar parasitic recoveries, suggesting that eosinophil peroxidase (EPO) is not required for host protection in this model (1). In order to investigate the role of the eosinophil granule proteins in host protection, we have now examined the course of Brugia pahangi infection in mice that have undergone targeted muta-

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two independent occasions, we injected groups of EPO+/− (n = 7) and WT (n = 8) mice with B. pahangi L3 and necropsied them on day 14. The absence of EPO does not impair the ability of the mice to eliminate the parasites, since both groups of mice have nearly identical worm recoveries (11.14% ± 6.4% in EPO−/− mice versus 11.75% ± 8.1% in WT mice; P = 0.86). Eosinophil numbers were significantly lower in EPO−/− than in WT mice [(3.2 ± 2.1) × 10^6 eosinophils/mouse in EPO−/− mice versus (5.9 ± 2.0) × 10^6 eosinophils/mouse in WT mice; P < 0.01], though total PEC numbers were comparable. Data from the duplicate experiment were similar.

MBP−/− mice also did not manifest a defect in their ability to eliminate infection. We injected 50 B. pahangi larvae into each of five mice. The larval recoveries from these mice were comparable to those from WT mice at 2 weeks (28.3% ± 18.8% in MBP−/− mice compared to 36.0% ± 12.9% in WT mice; P = 0.72). In another experiment, the recoveries were lower in both strains of mice but equivalent (0.5% ± 0.5% in MBP−/− mice compared to 3.75% ± 1.9% in WT mice; P = 0.1). PEC numbers were comparable between the two groups. Unlike EPO−/− mice, MBP−/− mice did not have a defect in eosinophil numbers. However, the side-scatter profile (representing granularity or complexity) of eosinophils measured by flow cytometry was significantly lower in the MBP−/− eosinophils, reflecting a substantial contribution by this one protein for this parameter (data not shown).

In summary, treatment with the anti-CCR3 antibody was consistently associated with higher worm recoveries than was isotype control treatment, and this increase in worm recovery was associated with a significant and selective depletion of eosinophils. The results from the two approaches seem to suggest that eosinophils do play an important and nonredundant role in the elimination of the parasite. Our results also suggest that neither EPO nor MBP−1, the two most abundant eosinophil secondary granule proteins, is crucial in worm elimination. It is likely that the repertoire of eosinophil granule contents is redundant and that the absence of one particular protein is compensated for by the other(s). Likewise, in a murine model for airway hyperreactivity, in which these mice were originally studied, the absence of either one of these granule proteins failed to affect the airway response (6, 7).

An unexpected finding for the EPO−/− mice was that their eosinophil numbers were about half of those in WT mice. It is not yet clear how EPO might regulate eosinophil survival or recruitment. It is still possible that the defect in eosinophil numbers is due to an artifactual defect unrelated to EPO function.

Our data argue that eosinophils are required for optimal clearance of B. pahangi larvae from the peritoneal cavity following a primary infection and that this eosinophil-mediated protection is not abrogated by the absence of EPO or MBP−1.

REFERENCES


