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The cost of parasitic worms to humanity in the world today is high, with 2 billion people estimated to be infected. These multicellular eukaryotes are highly adapted to their hosts, often causing chronic infection. Reinfection is common as well, and the development of inexpensive, stable, and effective vaccines or therapies to control parasitic worm infections has been challenging. As discovery of new anthelmintic drugs has diminished and drug resistance in worms has emerged, effort has been refocused on understanding host immunity. Benefits of the research have been far reaching, with new mechanisms and mediators revealed, many with significance in other diseases, including allergy (1) and obesity (2). Murine models of helminth infection have been powerful tools in these efforts. Several nematodes that are natural parasites of rodents are used, including the whipworm *Trichuris muris*, the hookworm *Nippostrongylus brasiliensis*, the filarial worm *Litomosoides sigmodontis*, and the gut-dwelling *Heligmosomoides polygyrus*, as well as the human pathogen *Trichinella spiralis*. Of particular note is the impact of research that has been conducted in the murine model of *Schistosoma mansoni*. For >50 y, discoveries from *S. mansoni*-infected mice have been transformative in advancing our understanding of host defense to this important group of pathogens.

Mast cells, eosinophils, and IgE are prominent in antihelminth responses. Documentation of the influence of a lymphocyte-derived soluble factor on eosinophilia in *T. spiralis*-infected rats (3) and the identification of this factor as IL-5 in *S. mansoni*-infected mice (4) bracketed a period of intense investigation of the genetic basis for resistance and susceptibility to worm infection in inbred mouse strains. This was coincident with an explosive advancement of our understanding of cytokines as the messengers used by T cells to tell the intestine has been shown in several models to be mediated by various Th2-dependent mechanisms (18). Thus, it is clear that there are important distinctions among immune responses required to eliminate worms from different habitats and, furthermore, that understanding these differences is crucial to the development of effective therapies and vaccines.

This report and the follow-up study by Grzych et al. (19) established schistosome eggs and the soluble egg Ag (SEA) as prototypical Th2 Ags. The hunt was on for the components of SEA that triggered the response, as well as the mechanism(s) underlying the effect. It was shown that SEA inhibits production of IL-12 by dendritic cells and is processed via a cellular pathway that is distinct from that of the strong Th1-inducing *Propionibacterium acnes* (20). The identity of a component of SEA responsible for Th2 cell activation was elusive. Recently, a RNase in SEA, called omega-1, has been reported to influence dendritic cells to induce differentiation of Th2 cells (21, 22). Other important perspectives on initiation of infection was demonstrated in the mouse model of disease caused by the intracellular protozoan parasite, *Leishmania*. IFN-γ production was known to correlate with resistance (7), and Th1, but not Th2, cells were shown to be protective (8–10). This work set the course for our current understanding of IL-12, Th1 effector cells, IFN-γ, and classically activated macrophages in host defense against intracellular pathogens, which is established as a paradigm in immunology textbooks. In contrast, the natural history of Th2-mediated immunity has been revealed more gradually, and its real purpose continues to be actively debated (11, 12).

Experiments described by Pearce et al. (13) in this issue’s *Pillars of Immunology* revealed that mice infected with *S. mansoni* mount Th1 responses during the first few weeks of infection, but this response shifts to a Th2 response after 8 wk, a time at which adult worms begin to lay eggs. Specifically, the authors showed that T cell-derived cytokine production changed from predominantly IFN-γ and IL-2 to IL-5 and IL-4 at the onset of patency. Injection of eggs into mice that had been vaccinated with *S. mansoni* cercariae, and were mounting host-protective Th1 responses, induced the same shift. The evidence supported the conclusion that a Th2 response during primary infection with *S. mansoni* preserves the parasite, supports patency, and promotes transmission. Subsequently, it was documented that IL-4–deficient, *S. mansoni*-infected mice die of overwhelming Th1 responses and high levels of NO, confirming a pivotal role for IL-4 in preserving both host and parasite (14). Thus, the benefit to the host of its own survival is attached to the cost of continued shedding of eggs and perpetuation of the parasite in the environment and host population. In recent years, additional examples of Th2 responses that support parasitic worm survival have been described for other tissue-dwelling worms (15–17). In contrast, effective clearance of worms that colonize the intestine has been shown in several models to be mediated by various Th2-dependent mechanisms (18).

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Abbreviation used in this article: SEA, soluble egg Ag.

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of Th2 immunity have been provided by reports that innate responses involving IL-4 and alternative macrophage activation are induced by hookworms and filarial nematodes (23, 24). Recently, lymphocyte-lineage–negative nuocytes, operating in an innate context, were shown to impact the outcome of hookworm infection (25). Cytokines released from injured tissue cells, most prominently IL-33 and IL-25, cause nuocytes to produce IL-13, which upregulates goblet cell expression of Relmβ, a key mediator of expulsion of hookworms. Other innate cells, including eosinophils, basophils, and mast cells, also produce IL-4, IL-5, and IL-13 (26). Thus, innate responses that parallel or complement the Th2 response play important roles in host defense.

Following the discovery of IL-13 (27–29) and the first proposal for the paradigm of alternative macrophage activation (30), further investigation of Th2 responses during chronic infection with S. mansoni revealed that IL-13 is central to the development of fibrosis and the granulomatous response to eggs in the liver (31, 32). These responses are induced by living eggs that cause tissue injury, and the growing consensus is that Th2 cytokine-dependent, alternatively activated macrophages are central to wound healing in a variety of infectious and noninfectious processes (11, 12).

Cross-inhibition of Th1 and Th2 responses lasted only a short time as a complete explanation for regulation of Th responses. Immediately following the report of Pearce and coworkers (13), the same group showed that IL-10 was an important inhibitor of both Th1 and Th2 responses in S. mansoni–infected mice (33, 34). IL-10 inhibits NO production in S. mansoni (35) and other worm infections, modulating the toxicity and supporting the survival of parasites (15, 36). Eventually described as a central mediator of regulatory T cells, the significance of IL-10 (and other inhibitory cytokines and receptors) in immune regulation extends beyond the context of helminth infection. The potential for application of infection-induced regulatory effects to therapy for other diseases was demonstrated when Trichuris infection was shown to cause improvement in patients suffering from inflammatory bowel disease (37–39). Experimental infections with helminths, when combined with murine models of autoimmune and allergic disease (37–39), have begun to reveal the regulatory mechanisms involved in these effects. Not all regulators are Th lymphocytes; it has been reported that both humans and mice infected with schistosomes have select populations of IL-10–producing B lymphocytes (40, 41). Schistosome-induced IL-10 correlates with resistance to, or absence of, allergy symptoms in children (40, 42), a finding that provides support for Strachan’s (43) “hygiene hypothesis” as an explanation for the increasing prevalence of allergic diseases. An additional benefit of Th2 immunity has been suggested to occur when mild Th2 effector responses to toxic environmental substances provoke avoidance behaviors that would reduce the risk of life-threatening exposure to harmful agents (12). Although the global and individual costs of parasitic worm infection are significant, a growing body of evidence supports an immunologic benefit associated with infection. Reducing the risk of uncontrolled inflammation and limiting the tissue damage caused by injury are important features of host defense against large, destructive pathogens, but would be beneficial in a variety of other diseases. Devising ways to exploit the benefits of immunity to worm infection, in the absence of the costs, is the challenge we face today.

Disclosures
The author has no financial conflicts of interest.

References


