REGULATION OF PATHOGENESIS AND IMMUNITY IN HELMINTH INFECTIONS

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Annotation: This article provides information on the pathogenesis of gelmint infections and the regulation of immunity.

Keywords: T helper (Th), Helminth Infections , regulatory T (T reg) , signal transducer and activator of transcription (STAT)-6

It is widely accepted that helminths and their antigens inherently induce T helper (Th) 2 responses, and it is likely that Th2 immunity evolved in response to infections with these parasites. In February 2009, scientists from 32 countries assembled in Tahoe City, CA for the Keystone symposium on Pathogenesis and Immune Regulation in Helminth Infections (February 1–5, 2009), organized by Rick Maizels, Maria Yazdanbakhsh, and Thomas Wynn, to discuss how immune responses develop in response to helminth infections and how these infections are (or are not) controlled. The discussions provided new insights into the cellular players, cytokines, and effector molecules that help initiate, and subsequently limit, immune responses during helminth infection. How the human immune system fights off—or learns to live with— worm infections has been extensively studied, but many questions remain unanswered. On the host side, the coordinate functions of multiple cell types, including phagocytes, granulocytes, B cells, Th2 cells, and regulatory T (T reg) cells, dictate the outcome of infection. Getting things started: Th2 cells and beyond IL-4–producing Th2 cells are perhaps the most extensively studied cells in the context of worm infections, and generating an effective Th2 response has long been thought to require the early production of interleukin (IL)-4. Contrary to this idea, however, Graham Le Gros (Wellington, New Zealand) showed that neither IL-4 nor signal transducer and activator of transcription (STAT)-6, a key component of the IL-4R signaling pathway, was essential for the

development of a Th2 response in vivo. Activation of an IL-4– linked GFP reporter construct was intact in STAT-6–deficient mice infected with Nippostrongylus brasiliensis (King et al., 2008; van Panhuys et al., 2008), suggesting that other factors, whether host- or parasite-derived, are critical for Th2 polarization in vivo. Another Th2-inducing cytokine, thymic stromal lymphopoietin (TSLP), may also be dispensable for generating Th2 responses against certain helminth infections. In noninfectious settings, such as allergy, Th2 responses are largely TSLP dependent. But in the absence of a functional TSLP receptor, mice infected with Heligmosomoides polygyrus, N. brasiliensis, or Schistosoma mansoni (Fig. 1). still generated strong Th2 responses (Nicola Harris, Lausanne, Switzerland; Massacand et al., 2009; Ramalingam et al., 2009). This rule does not hold true for all worm infections, however, as TSLP is essential for the development of Th2 responses against Trichuris muris (Taylor et al., 2009a). A key difference between these parasites appears to be the ability of H. polygyrus and N. brasiliensis, but not T. muris, to inhibit the production of inflammatory cytokines, such as IL-6, IL-12, and TNF, from dendritic cells (DCs) in response to Toll-like receptor (TLR) ligation. T. muris may thus require TSLP to help restrain IL-12 production before a Th2 response can develop, whereas other parasites inhibit cytokine production directly, thereby circumventing this pathway. Where and how Th2 cells are generated has been the subject of intense scrutiny. Using IL-4-GFP (“4get”) reporter mice to track cells that produce IL-4 in response to infection, multiple groups have found that follicular T helper (Tfh) cells are the predominant IL-4–producing cells in responding lymph nodes (Richard Locksley, San Francisco, CA and Edward Pearce, Saranac Lake, NY; Reinhardt et al., 2009; Zaretsky et al., 2009). Similar findings have also been reported by Markus Mohrs (King and Mohrs, 2009). This may not seem surprising, considering the well-established role of IL-4 in B cell activation and Ig class switching, but it nevertheless raised questions about the precise definition of a Th2 cell. Locksley argued that conventional Th2 cells may function primarily within tissues to mediate classical allergic-like inflammation, such as eosinophil recruitment, whereas Tfh cells

function in the follicles to deliver help to B cells. Pearce offered further perspective on the Th2 population in Schistosoma infection by showing that Th2 cells lose responsiveness as chronic disease develops, a process mediated by increased expression of GRAIL, an E3 ubiquitin ligase implicated in the development of T cell anergy (Taylor et al., 2009b). These and other studies have taught us a great deal about the host requirements for generating Th2 responses against helminths. But far less is known about what components of the parasitesare required to initiate the host response. New data from Markus Mohrs (Saranac Lake, NY) revealed that the Th2-inducing potential of schistosome eggs is due in part to the action of omega-1, a glycoprotein with ribonuclease activity that is released from eggs under physiological conditions (Everts et al., 2009). Purified omega-1 induced strong Th2 responses in mice, even in those lacking the IL-4 receptor. Omega-1 also inhibited DC activation in response to lipopolysaccharide, suggesting that the egg protein acts at the initial stages of response (Steinfelder et al., 2009). Production of omega-1 likely helps sustain infection, as the subsequent Th2 response stimulates the formation of protective granulomas around the eggs. The hunt is now on to identify the cellular receptor for omega-1. Like most helminth infections, schistosomiasis elicits a predominant CD4+ Th2 cell response, and mice depend on this response to survive infection. In the absence of IL-4, mice develop hepatotoxicity, endotoxemia, and severe cachexia, which together contribute to the death of the animal. However, some strains of mice, such as CBA, are more prone to developing Th1 and Th17 responses, and thus develop severe pathology in response to S. mansoni infection (Miguel Stadecker and Mara Shainheit, Boston, MA). DCs from CBA mice produced more IL12p40 and IL-6 in response to live schistosome eggs than did DCs from C57BL/6 mice. CBA DCs also stimulated stronger IL-17 production from transgenic T cells specific for the egg antigen Sm-p40. In vitro experiments suggested that the increased Th17 response requires both IL-1 and IL-23 (Rutitzky et al., 2008) and that the Th17 response is responsible for the severe egg-induced inflammatory response seen in infected CBA mice (Shainheit et al., 2008). Co-infection with the intestinal

nematode H. polygyrus decreased IL-17 and interferon (IFN)- production in CBA mice, perhaps helping to explain the low incidence of autoimmune diseases in regions where helminth infections are endemic (Bazzone et al., 2008).

Keeping potentially dangerous Th1 responses at bay in T. muris infection depends on activation of the NF-B signaling pathway in intestinal epithelial cells (IECs), according to David Artis (Philadelphia, PA). In mice with an IEC-specific ablation of the classical NF-B pathway, DCs produced excess inflammatory cytokines leading to the development of a nonprotective Th1 response (Zaph et al., 2007). Normally, the DC-triggered induction of a Th2 response depends on the NF-B–dependent production of TSLP and IL-25 from IECs (Zaph et al., 2008; Taylor et al., 2009a).

Applying the brakes: T reg cells Generating a Th2 response to parasite infections is essential, but controlling that response is equally imperative. Some of this control is provided by T reg cells, which were shown to dampen Th2 responses during H. polygyrus infection (Rick Maizels, Edinburgh, Scotland, UK; Wilson et al., 2005). In this model, the parasite itself drives the differentiation of T reg cells from naive CD4+ T cells by secreting a product that binds to host TGF- receptors. Inhibiting this interaction in vivo decreased the intensity of infection, presumably as a result of more effective Th2 responses, illustrating the evolutionary advantage of this pathway for the parasite. Induction of T reg cells is also needed for Litomosoides sigmodontis to establish long-lasting infections. When T reg cells were depleted in susceptible mouse strains, infection was cleared (Nienke van der Werf and Matthew Taylor, Edinburgh, Scotland, UK; Taylor et al., 2009). In chronic infection, subsequent reactivation of hyporesponsive Th2 cells, which express high levels of GITR, CTLA-4, and PD-1, required CTLA-4 blockade or co-stimulation of the cells through GITR. Indeed, GITR ligation was essential for the development of Th2 responses during this infection. Recent data indicates that GITR also promotes the generation of Th2 responses during the initial immune-priming stage of infection and that blocking the PD-1 pathway enhances parasite

killing, illustrating the opposing roles of these pathways in anti-helminth immunity. T reg cells also suppress host immune responses in humans, presumably allowing parasites to establish chronic infections (Maizels and Yazdanbakhsh, 2003). Indeed, schistosome-infected individuals in Gabon had increased numbers of circulating T reg cells compared with their uninfected neighbors (Maria Yazdanbakhsh, Leiden, Netherlands and Ayola Akim Adegnika, Lambaréné, Gabon). And helminth-induced T reg cells may have more potent suppressive activity than those from healthy individuals. T reg cells from geohelminthinfected individuals in Indonesia, for example, were more effective at suppressing proliferation and IFN-□ production by effector T cells in response to malaria antigens and BCG than T reg cells from healthy individuals (Yazdanbakhsh and Taniawati Supali, Jakarta, Indonesia). Tom Nutman (Bethesda, MD) also reported diminished production of cytokines in response to malaria antigens in peripheral blood cells from helminth/malaria coinfected individuals. This inhibition was driven primarily by the suppressive cytokine IL-10.

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