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In the originally published version of this article, the authors wrote "Helminth infection is typically associated with increased numbers of Treg cells, and depletion of Treg cells promotes the chronicity of *Stronglyoides ratti* (Blankenhaus et al., 2011), whereas enhancing Treg cell numbers by using IL-2-anti-IL-2 mAb2 immune complexes results in the accelerated expulsion of *H. polygyrus* (Smith et al., 2016)."

However this should read, "Helminth infection is typically associated with increased numbers of Treg cells, and depletion of Treg cells promotes resistance against *Stronglyoides ratti* (Blankenhaus et al., 2011), whereas enhancing Treg cell numbers by using IL-2-anti-IL-2 mAb2 immune complexes results in increased worm burdens following *H. polygyrus* infection (Smith et al., 2016)."

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Review

Recent Advances in Type-2-Cell-Mediated Immunity: Insights from Helminth Infection

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Type-2-cell-mediated immune responses play a critical role in mediating both host-resistance and disease-tolerance mechanisms during helminth infections. Recently, type 2 cell responses have emerged as major regulators of tissue repair and metabolic homeostasis even under steady-state conditions. In this review, we consider how studies of helminth infection have contributed toward our expanding cellular and molecular understanding of type-2-cell-mediated immunity, as well as new areas such as the microbiome. By studying how these successful parasites form chronic infections without overt pathology, we are gaining additional insights into allergic and inflammatory diseases, as well as normal physiology.

Introduction

The majority of wild vertebrates harbor parasitic helminths (Dobson et al., 2008), the most common of which are intestinal nematodes (or soil-transmitted helminths) that live as adult worms within the intestines for prolonged periods (Bethony et al., 2006). Tissue-dwelling helminths such as trematodes and filarial nematodes are also medically important parasites that cause widespread disease (King and Dangerfield-Cha, 2008; Taylor et al., 2010). Their ubiquitous presence in our evolution exerts a powerful force of selection on our immune system (Fumagalli et al., 2009), although they are now eradicated to a large extent within westernized human populations. Still, over one billion people worldwide, mainly children, are infected by helminths (Hotez et al., 2008). Although the majority of people carry low-level infections that are typically asymptomatic, pathology can occur in heavily infected individuals harboring very high parasite burdens. But because so many people are infected, disease within even a small minority results in a loss of disability-adjusted life years (DALYs) that is greater than that estimated for malaria and approaches that attributed to tuberculosis (Bethony et al., 2006; King and Dangerfield-Cha, 2008). Superinfected individuals that are unable to expel the parasites can have particularly weak responses to these organisms; however, at the other end of the disease spectrum, individuals with an over-exuberant immune response can succeed in eliminating the parasites but suffer consequences of immune-mediated pathology and collateral damage (Hotez et al., 2008).

Regardless of the site of colonization (which varies tremendously), infection with all helminths is strongly associated with type-2-cell-mediated immunity in organisms from jawed fish to mice to humans (Maizels and Yazdanbakhsh, 2003). Type-2-cell-mediated immune responses play a role in both "resistance" (Grencis, 2015) and "tolerance" (Medzhitov et al., 2012) mechanisms during helminth infections. Resistance mechanisms promote the expulsion of helminths and the prevention of reinfection and ensure that parasitic burdens do not become high enough to be detrimental to host survival. Tolerance mechanisms (e.g., wound healing and resolution of pro-inflammatory responses) can reduce the impact of helminths on host fitness without directly affecting worm burden. Carrying a small number of helminths could be a less detrimental strategy than the consequences of immunopathology. Hence, in the setting of natural infections, the majority of hosts carry a small number of helminths, such that the type-2-cell-mediated immune response maintains a balance between resistance and tolerance mechanisms and thereby benefits both the host and parasite. Of note, most parasites secrete an array of immune-modulatory products that encourage coexistence with their host and allow parasite chronicity (Maizels and Yazdanbakhsh, 2003).

Immunologists have long believed that type-2-cell-mediated immunity evolved as a response to helminth parasites, yet the discovery of an increasing number of roles for type-2-cell-mediated innate immune responses (i.e., those mediated by innate lymphoid cells and myeloid cells) in the absence of infectious stimulation challenges this view. Neonates are born with an immature immune system that is skewed toward type-2-cell-mediated responses (Torow et al., 2017), and evidence indicating a physiological role of type-2-cell-mediated immunity in mediating perinatal adaptation is emerging from reports that IL-33 production (which results in type-2-cell-derived cytokine production and eosinophil recruitment) during the first days of life contributes to the establishment of lung homeostasis (Saluzzo et al., 2017) and to license thermogenesis (Odegaard et al., 2016). A close association between innate type-2-cell-mediated immunity and tissue homeostasis and wound repair, whereby type-2-cell-derived cytokines stimulate macrophages to adopt an alternatively activated macrophage (AAM) phenotype and to express genes involved in tissue repair, is also evident (Knipper et al., 2015). AAMs and/or eosinophils are now appreciated to play important roles in mammary gland development (Gouon-Evans et al., 2002) and promote the regeneration of skeletal muscle (Heredia et al., 2013) and liver tissue (Goh et al., 2013). Lastly, type-2-cell-mediated immunity now has well-defined roles in limiting type 1 inflammation following bacterial infection (Blériot et al., 2015). Of note, many responses designed to protect barrier tissues from damage, such as the production of mucus and epithelial repair proteins, are elicited by type-2-cell-mediated immunity (Finkelman et al., 2004).

Thus, innate type-2-cell-mediated immunity could have evolved to regulate perinatal adaptation, to protect and repair tissues, and to regulate inflammation. However, these same cellular mechanisms could have been co-opted by the parasite to promote tolerance mechanisms, thus avoiding collateral damage to either the host or the parasite. In contrast to these innate type 2 cell responses, adaptive type-2-cell-mediated responses could have arisen in response to continuous pressure from these environmentally ubiquitous organisms, and they offer an advantage to the host by limiting the acquisition of large parasite burdens resulting from frequent recurrent infections. Some helminths have additionally evolved the ability to promote regulatory T (Treg) cell responses that dampen the type-2-cell-mediated response. An appropriate balance of type-2-cell-mediated responses and Treg cell responses allows the expulsion of some but not all of the parasites within the host, resulting in a state whereby infected individuals harbor worm loads that fall below the threshold required to cause disease.

The most widely used murine models for intestinal nematodes include *Trichuris muris* (Klementowicz et al., 2012), *Nippostrongylus brasiliensis*, and *Heligmosomoides polygyrus* (Camberis et al., 2003). *Trichuris muris* is closely related to the human whipworm, *Trichuris trichiura*, and has been used for determining many intestinal mechanisms associated with host resistance and susceptibility. *N. brasiliensis* and *H. polygyrus* belong to the Strongylida order, which includes the human hookworm parasites *Ancylostoma duodenale* and *Necator americanus*. Although *N. brasiliensis* provides an acute model for the life cycle of the human hookworm, including skin penetration and lung migration prior to entrance into the intestinal lumen, this parasite fails to persist and is expelled from immune-competent animals. By contrast, primary infections with *H. polygyrus* can persist for many months and thus represent a useful model for chronic intestinal helminthiases. Murine models of *Schistosoma* infection have been widely used for studying granuloma formation, macrophage function, fibrosis, and immune regulation (Barron and Wynn, 2011).

Many fundamental discoveries have resulted from studies on helminth infections, including the identification of innate lymphoid type 2 cells (ILC2s) (Fallon et al., 2006; Moro et al., 2010; Neill et al., 2010; Price et al., 2010) and tuft cells (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2016) as key players in type-2-cell-mediated responses. Helminth models have also unveiled important effects of type-2-cell-mediated immunity on host physiology, including a role for AAMs in tissue repair (Chen et al., 2012). Here, we review some recent advances, including the evolution of type-2-cell-mediated immunity, initiation of type-2-cell-mediated responses, mechanisms of parasite resistance and tissue repair, and the impact of host-parasite interactions on metabolic status and the microbiome.

Induction of Type-2-Cell-Mediated Immunity

Despite their importance in both health and disease, the mechanisms by which type-2-cell-mediated immune responses are induced have remained ill defined. Type-2-cell-mediated immunity is characterized by the production of interleukin-4 (IL-4), IL-13, and IL-5, resulting in B cell isotype switching to IgE and IgG1 (mice) or IgG4 (humans), eosinophil and basophil hematopoiesis, expansion and activation of AAMs and mast cells, and goblet cell hyperplasia (Finkelman et al., 2004). Both ILC2s and $CD4^+$ T helper 2 (Th2) cells are important sources of type-2-cell-derived cytokine production (Fallon et al., 2006; Moro et al., 2010; Neill et al., 2010; Yasuda et al., 2012), although other innate cells, including mast cells, basophils, eosinophils, and invariant natural killer T (iNKT) cells that are capable of producing IL-4, can contribute.

The infection of mice with helminths that elicit strongly polarized type-2-cell-mediated immune responses has led to the identification of several epithelial cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), as early players in the response (Humphreys et al., 2008; Massacand et al., 2009; Owyang et al., 2006; Taylor et al., 2009; Zaph et al., 2007) (Figure 1). IL-25 is produced by epithelial cells in response to infection (Humphreys et al., 2008; Owyang et al., 2006) and can also be produced by Th2 cells (Fort et al., 2001). IL-25 is necessary for protective immunity against *T. muris* (Owyang et al., 2006), *N. brasilienis* (Price et al., 2010), and *H. polygyrus* (Zaiss et al., 2013), and the injection of recombinant IL-25 into naive mice stimulates the production of type 2 cytokines by ILC2s (Fallon et al., 2006; Price et al., 2010), induces IL-4 production by iNKT cells (Terashima et al., 2008), and promotes Th2 cell differentiation (Wong et al., 2007).

IL-33 (a member of the IL-1 family) is also essential for protective immunity in response to many (Hung et al., 2013; Humphreys et al., 2008; Scalfone et al., 2013) but not all (Zaiss et al., 2013) helminths. This cytokine is stored in the nucleus of epithelial cells at barrier sites such as the epithelial, lung, and intestinal tissue (Schmitz et al., 2005) and is released after damage-induced cellular necrosis. After its release, IL-33 binds to its receptor, ST2 (suppression of tumorigenicity 2), to activate a wide range of immune cells and elicits the production of type 2 cytokines by ILC2s (Schmitz et al., 2005), Th2 cells (Kurowska-Stolarska et al., 2008; Matsuba-Kitamura et al., 2010; Schmitz et al., 2005), basophils, and mast cells (Ho et al., 2007; Kondo et al., 2008) (Figure 1).

TSLP promotes Th2 cell differentiation and cytokine production and can act on a wide array of immune cells, including dendritic cells (DC), monocytes, granulocytes, T cells, and B cells (Ziegler and Artis, 2010). Although IL-25 and IL-33 play crucial roles in promoting ILC2 responses in the lung and intestine, the activation of ILC2 responses in the skin is uniquely dependent on TSLP (Kim et al., 2013). Mice deficient in the receptor for TSLP are susceptible to *T. muris* infection (Taylor et al., 2009); however, they develop normal type-2-cell-mediated immunity after infection with *N. brasiliensis* or *H. polygyrus* (Massacand et al., 2009). Antibody blockade of IL-12p40 or interferon-γ (IFN-γ) in TSLP-receptor-deficient mice after *T. muris* infection renders this susceptible strain resistant (Massacand et al., 2009; Taylor et al., 2009; Zaph et al., 2007), indicating that the main function of TSLP in the intestine is not to directly promote type-2-cell-mediated immunity but rather to limit the development of type 1 responses (Figure 1). Of note, *N. brasiliensis*- and *H. polygyrus*-secreted products can directly block IL-12p40 production by DCs (Massacand et al., 2009), a finding that supports the hypothesis that type-2-cell-mediated immunity is the preferred outcome for some parasites.

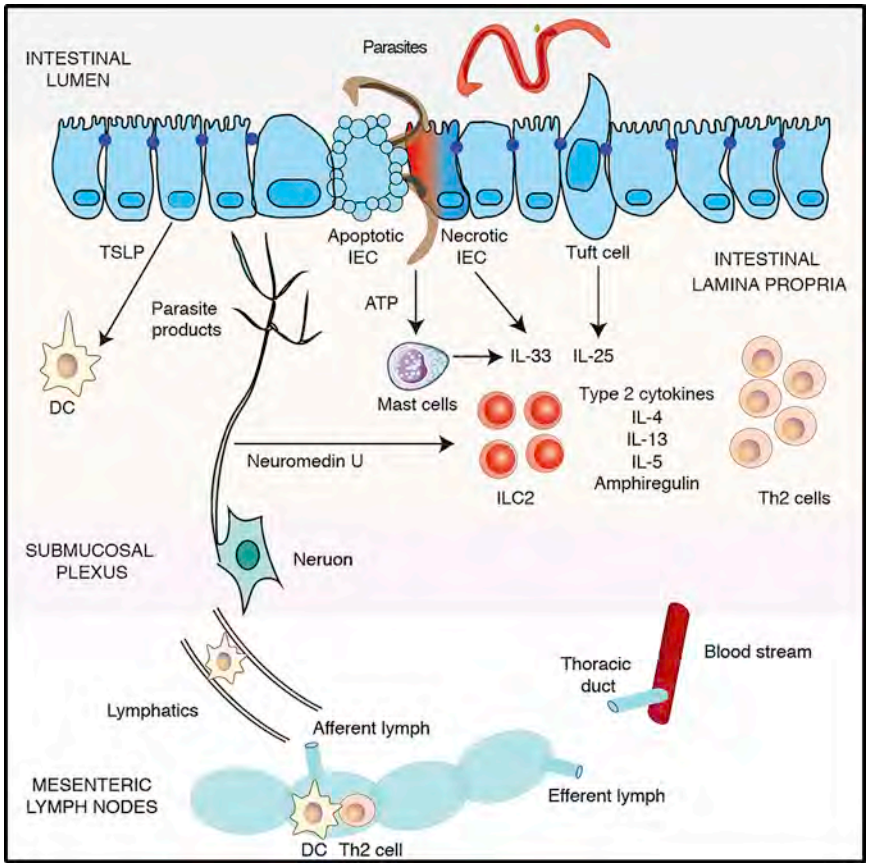

Figure 1. Induction of Type-2-Cell-Mediated Responses by Intestinal Helminths

The entry of parasites into the intestine can trigger IEC necrosis and the release of IL-33. Alternatively, IECs can undergo apoptosis and release ATP, which stimulates mucosal mast cells to produce IL-33. Tuft cells also respond to parasites and produce IL-25. Together, IL-25 and IL-33 elicit the activation of ILC2s, which produce an array of type-2-cell-derived cytokines, including IL-13, IL-5, amphiregulin, and in some cases IL-4. The production of cytokines by ILC2s is further amplified by the release of NMU from neurons that respond directly to helminth products. Although not depicted, ILC2-derived IL-4 and/or IL-13 promotes tuft cell expansion and further IL-25 production, which also amplifies the type-2-cell-mediated response. IECs also respond to helminths by producing TSLP, and TSLP together with parasite products triggers DCs to migrate to the draining mesenteric lymph nodes and activate Th2 cells. Th2 cells in the lymph nodes are located in the B cell follicles and produce IL-4 and support B cell expansion and IgG1 and IgE production. Other Th2 cells leave the lymph nodes and circulate back to the intestinal lamina propria, where they produce an array of type 2 cytokines and also sustain the ILC2 response. Cytokine production by ILC2s and Th2 cells acts locally to promote the expulsion of adult worms from the intestinal lumen.

More recently, additional roles for tuft cells, mast cells, and neurons as initiators or amplifiers of intestinal type-2-cell-mediated responses have been unveiled. Tuft cells represent a specialized intestinal epithelial cell (IEC) whose function(s) had remained largely unknown before the publication in 2016 of three new studies (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2016) showing that these cells represent the sole intestinal source of IL-25 produced in response to intestinal helminth infection. Tuft-cell-derived IL-25 is necessary for activating IL-13 production by ILC2s, further promoting tuft cell expansion and providing an early positive-feedback loop that amplifies the type-2-cell-mediated response. Of note, Howitt et al. (2016) have demonstrated a requirement for signaling to tuft cells via chemosensory taste receptors—raising the intriguing possibility that these cells use chemosensation to recognize helminths.

Mast cells have been historically viewed as effector cells that can be activated by IgE to promote the expulsion of *Strongyloides venezuelensis* (Lantz et al., 1998) and *T. spiralis* (Knight et al., 2000). More recently, a role for these cells as initiators of type-2-cell-mediated immunity has been reported (Hepworth et al., 2012; Shimokawa et al., 2017). In the study by Shimokawa et al. (2017), mast cells were identified as a key source of IL-33 after *H. polygyrus* infection following the activation of these cells by extracellular ATP released from apoptotic epithelial cells damaged during the invasion of the intestinal wall by *H. polygyrus* larvae (Figure 1). IL-33 can also elicit IL-9 production by ILC2s (Mohapatra et al., 2016), and IL-9 increases the production of IL-2 by mast cells, leading to further ILC2 expansion (Moretti et al., 2017) and providing a second positive-feedback loop.

Very recently, a series of reports identified the neuropeptide receptor *Nmur1* as being highly expressed on ILC2s and showed that stimulation of these cells with the NMUR1 ligand, neuromedin U (NMU), elicits production of IL-5 and IL-13 (Cardoso et al., 2017; Klose et al., 2017; Wallrapp et al., 2017), especially when delivered in combination with IL-25 (Wallrapp et al., 2017). In keeping with these findings, mice treated with NMU showed enhanced resistance against *N. brasiliensis*—whereas mice lacking *Nmur1*, specifically on ILC2s, harbored increased worm burdens (Cardoso et al., 2017; Klose et al., 2017). Intriguingly, neurons could directly sense helminth products in order to produce NMU, revealing that neuronal activation is an additional means by which helminths initiate type-2-cell-mediated immunity (Cardoso et al., 2017).

Together, these findings indicate that the coordinated action of many cell types—epithelial cells, chemosensory cells, mast cells, DCs, and neurons—promotes type-2-cell-mediated responses after a helminth infection. These studies also highlight how studies of helminth infection can contribute to our understanding of the cellular and molecular mechanisms governing type-2-cell-mediated immunity.

Expulsion of Adult Worms from the Intestines

The displacement of luminal-dwelling adult worms from the intestines is widely accepted to involve the impact of type-2-cell-mediated immunity on host physiology, including increases in intestinal contractility, electrolyte section, and

mucous production—collectively referred to as the "weep-and-sweep" response. This response not only promotes worm expulsion but also contributes to many of the symptoms associated with allergy, and helminth models have often been used to model allergic reactions. The most important initiators of the weep-and-sweep response are the canonical type-2-cell-derived cytokines IL-4 and IL-13. IL-4 signals through both the type I receptor (composed of IL-4Rα and the common gamma chain) and the type II receptor (composed of IL-4Rα and IL-13Rα1), whereas IL-13 can signal only through the type II receptor (Finkelman et al., 2004). As a consequence, these cytokines have both overlapping and distinct roles. IL-4 and/or IL-13 signaling results in increased epithelial cell electrolyte secretion and mucosal permeability (Finkelman et al., 2004). These cytokines also increase smooth muscle hypercontractility (Finkelman et al., 2004) via mechanisms involving the stimulation of enteric nerves (Zhao et al., 2003) and AAMs (Zhao et al., 2008). IL-4 and or IL-13 stimulation also drives goblet cell hyperplasia and alters both the quantity and type of mucus produced during helminth infection (Hasnain et al., 2013).

Key effector molecules involved in the expulsion of adult worms continue to be identified. The major intestinal mucin, Muc2, is necessary for the timely expulsion of *T. muris* (Hasnain et al., 2010), whereas Muc5Ac, which is induced in the intestine by IL-4 and/or IL-13 signaling, contributes to the expulsion of *T. muris*, *N. brasiliensis*, and *Trichinella spirilas* (Hasnain et al., 2011). IL-4 and/or IL-13 activation of goblet cells also leads to the production of resistin-like molecule β (Relm-β), which exerts protective effects against *N. brasiliensis* and *H. polygyrus* by directly interfering with parasite feeding (Herbert et al., 2009). Unlike *N. brasiliensis* and *H. polygyrus*, Relm-β does not contribute to the expulsion of *T. muris*, probably because this parasite actively penetrates and feeds on epithelial cells (Nair et al., 2008). Instead, displacement of *T. muris* involves increased IEC turnover driven by Th2 cell production of IL-13 (Cliffe et al., 2005) and amphiregulin (Zaiss et al., 2006). For reasons that are not clear, IL-13 is sufficient to expel *N. brasiliensis* and *T. muris*, but IL-4 appears to play a more dominant role in expelling *H. polygyrus*. One possibility is that AAMs play a more important role in the expulsion of *H. polygyrus*, and these cells might be more responsive to IL-4 than to IL-13.

The Activation and Functions of AAMs

Macrophages are key innate cells that respond to tissue-environment alterations, such as conditions driven by type-2-cell-derived cytokines produced in response to helminth infection. Tissue damage caused by helminth colonization elicits a rapid production of type-2-cell-derived cytokines by innate cells such as ILC2s, eosinophils, neutrophils, and basophils, instructing macrophages to adopt an AAM phenotype. The phagocytosis of apoptotic cells has been shown recently to be necessary for the appropriate activation of a tissue repair program in response to IL-4 and/or IL-13 stimulation (Bosurgi et al., 2017) (Figure 2). A key difference between this alternatively activated state and the state of classical macrophages (CMs), which are activated by the engagement of microbial pattern-recognition receptors and IFNs, is the use of arginine (Qualls and Murray, 2016). Whereas IFNs induce nitric oxide (NO) synthase, which metabolizes arginine to NO and citrulline, IL-4 induces arginase-1 (Arg1), which hydrolyzes arginine to ornithine and urea (Rath et al., 2014). Arg1 activity from AAMs can deplete arginine availability, restraining T cell function by amino acid starvation (Van de Velde et al., 2017). In liver granulomas during *S. mansoni* infection, macrophage Arg1 is important in preventing Th2 cells from causing too much fibrosis (Pesce et al., 2009a). Although the type-2-cell-mediated response causes fibrosis, the lack of this response is also lethal (Brunet et al., 1997) because AAMs represent important mediators of proper granuloma formation (Herbert et al., 2004).

Macrophages that respond to helminth infections can derive from tissue-resident macrophages seeded during fetal development or from inflammatory macrophages that enter the tissue from the blood as monocytes (Rückerl and Allen, 2014) (Figure 2). Depending on the cellular origin, distinct lineages of macrophages respond differently to type-2-cell-derived cytokines (Gundra et al., 2014). Different helminth infections will also induce the accumulation of AAMs of different origins depending on the site of infection and the systemic response. For example, *H. polygyrus* induces the expansion of tissue-resident AAMs in the peritoneal cavity (Jenkins et al., 2013), *Litomosoides sigmodontis* expands tissue-resident AAMs in the thoracic cavity (Jenkins et al., 2011), and *S. mansoni* induces monocyte-derived AAMs to form within liver granulomas surrounding parasite eggs (Girgis et al., 2014; Nascimento et al., 2014) (Figure 2). Complicating matters further, monocyte-derived AAMs can eventually acquire the phenotype of tissue-resident AAMs through a vitamin-A-dependent mechanism after a period of residency in tissues (Gundra et al., 2017). Different helminth infection models can thus be used for probing different lineages of AAMs in different tissue environments and dissecting the molecular and cellular processes needed for differentiation, activation, and function (Figure 2). Different tissue environments also have specific amplifiers for AAMs. In the lungs, surfactant protein A (SP-A) enhances AAM proliferation, whereas in the peritoneal cavity and liver, the complement component, C1q, performs an analogous function (Figure 2) (Minutti et al., 2017). Lastly, the ability of macrophages to proliferate in these peripheral tissues can be driven not just by type-2-cell-derived cytokines, such as IL-4 and IL-13, but also by IL-33 through a distinct mechanism (Jackson-Jones et al., 2016).

In addition to repairing tissue, the function of AAMs during helminth infection centers on killing parasitic larvae (discussed later) and regulating inflammation. AAMs produce a distinct set of chitinase-like proteins that regulate neutrophil function and IL-17 production by γδT cells (Sutherland et al., 2014), as well as resistin-like molecule (Relmα), which regulates Th2 responses (Nair et al., 2009; Pesce et al., 2009b). Programmed death ligand 2 (PD-L2), a ligand of PD-1, is also a marker of monocyte-derived AAMs (Loke and Allison, 2003) and might contribute to regulating Th2 responses (Huber et al., 2010; van der Werf et al., 2013). Additionally, AAMs can be a source of retinoic acid (Broadhurst et al., 2012) and can either expand thymus-derived Treg cells or promote the differentiation of inducible Treg cells at sites of inflammation. Although some AAM molecules induce IL-17 production, AAMs also contribute to resolving IL-17-driven inflammation and lung damage (Chen et al., 2012). Lastly, the extensive cross-talk and regulation

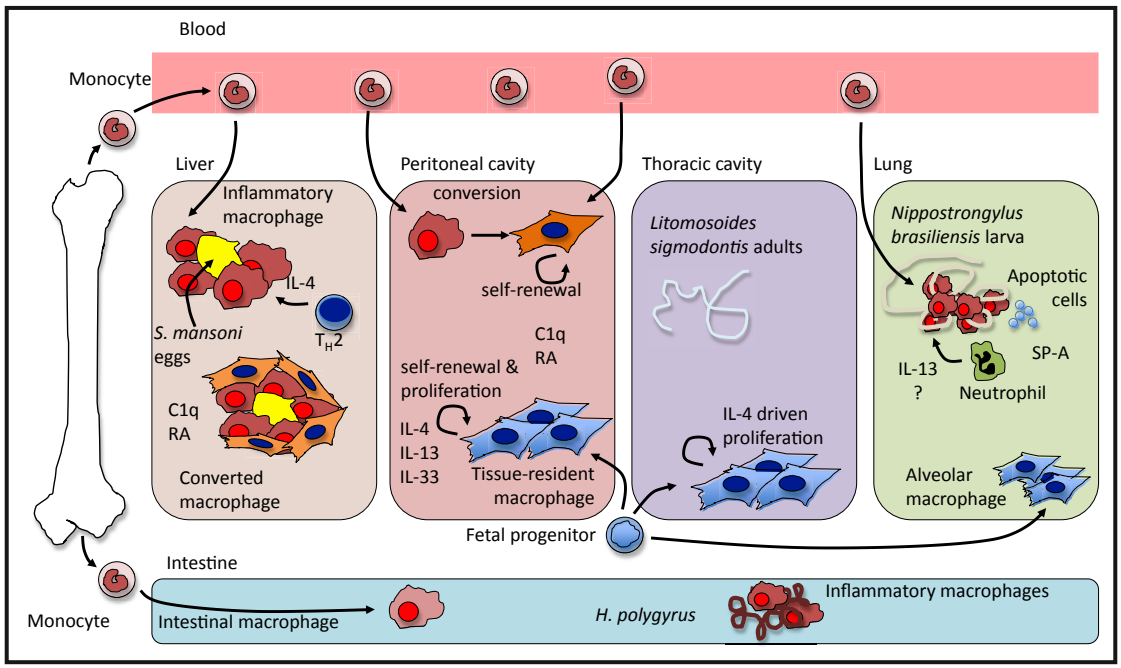

Figure 2. Induction and Functions of AAMs

Bone-marrow-derived monocytes circulate in the blood and enter different tissues during type-2-cell-mediated inflammatory responses and differentiate into monocyte-derived macrophages that are alternatively activated by IL-4 and/or IL-13 in the different tissues. Fetal progenitors that seed various tissues during embryonic development are self-renewing in the tissues but can be stimulated to proliferate by the type-2-cell-derived cytokines IL-4 and IL-13, as well as by IL-33. Concurrently, these progenitors become alternatively activated to express canonical AAM genes, such as *Ym1* (also called *Chi3l3*), *Fizz1* (also called *Relma*), and *Arg1*. C1q has the capacity to amplify the activity of IL-4 for both proliferation and activation in the liver and the peritoneal cavity, whereas in the lungs, SP-A performs the same function. Apoptotic cells also synergize with type-2-cell-derived cytokines, especially in the lungs during *Nippostrongylus brasiliensis* larval migration, to enable appropriate alternative activation. Depending on the type of helminth infection, type-2-cell-derived cytokines will expand either monocyte-derived AAMs (e.g., in liver granulomas around *S. mansoni* eggs) or tissue-resident AAMs (e.g., in the thoracic cavity by *Litomosoides sigmodontis* or in the peritoneal cavity by *Heligmosoides polygyrus*). Although *H. polygyrus* resides in the small intestine, the type-2-cell-mediated response is strong enough to drive proliferative expansion of peritoneal tissue-resident AAMs. However, granulomas formed around *H. polygyrus* in the intestine, which can lead to the expulsion of these parasites, are probably derived from inflammatory monocyte-derived macrophages. Although the AAMs in the immature granulomas around *S. mansoni* eggs in the liver are derived from inflammatory monocytes, as the granuloma matures some of these monocyte-derived AAMs convert to a tissue-resident phenotype (e.g., upregulating expression of UCP1 and downregulating expression of PD-L2) through a mechanism reliant on vitamin A. Phenotypic conversion of monocytes into tissue-resident peritoneal macrophages can also occur under steady-state conditions, whereby they undergo self-renewal and eventually displace some fetal-derived tissue-resident peritoneal macrophages. In different tissues and during different helminth infections, the source of type-2-cell-derived cytokines varies considerably. In liver granulomas during chronic *S. mansoni* infection, Th2 cells are the predominant source of cytokines, whereas in the acute lung injury model of *N. brasiliensis*, larval migration Th2 cells, ILC2s, or (surprisingly) neutrophils can be sources of IL-4 and/or IL-13. In other tissues, systemic levels of type-2-cell-derived cytokines appear sufficient to drive AAM accumulation, e.g., in the peritoneal cavity during *H. polygyrus* infection.

between neutrophils and AAMs still needs to be better understood (Chen et al., 2014) (Figure 2).

Helminth-Induced Adaptive Immunity and Protective Mechanisms Targeting Tissue-Migrating Larvae

Although innate immune cells, such as ILC2s, contribute to parasite resistance, adaptive immunity is necessary for completely expelling most helminths and for preventing re-infection. By contrast, the activation of Treg cells promotes tolerance against the parasite, preventing overt host pathology.

Adoptive transfer of ILC2s into IL-13-deficient mice could drive the expulsion of *N. brasiliensis* (Fallon et al., 2006); however, infected RAG-deficient mice (which lack T cells) fail to sustain ILC2 numbers and do not fully expel adult parasites (Neill et al., 2010). Thus, T cells appear to be necessary for maintaining ILC2 responses, possibly reflecting the ability of Th2 cells to produce IL-25. Dialogue between Th2 cells and ILC2s appears to be a two-way street, given that MHC II surface expression by ILC2s has been shown to enhance Th2 responses and promote full resistance against *N. brasiliensis* (Oliphant et al., 2014). For parasites that form chronic infections, such as *T. muris* and *H. polygyrus*, ILC2 expansion is minimal, although they do generate Th2 cells (Humphreys et al., 2008; Urban et al., 1991; Zaiss et al., 2013). Of note, *H. polygyrus* excretory secretory products contain factors that inhibit IL-33 production (McSorley et al., 2014) and elicit IL-1β to limit ILC2 expansion (Zaiss et al., 2013); thus, limited ILC2 expansion in infected mice could reflect an ability of this parasite to interfere with host immunity.

DCs are necessary for the induction of adaptive immune responses in the draining lymph node (Phythian-Adams et al., 2010; Smith et al., 2012); however, the mechanisms by which DCs promote type-2-cell-mediated immunity remain ill defined. Regulation of DC-Th2-cell interactions in the context of allergy has been recently reviewed elsewhere (Lambrecht and Hammad, 2009). In response to *H. polygyrus* infection, Th2-inducing DCs present in the draining mesenteric lymph node of infected mice expressed CXCR5 on their surface, a chemokine receptor responsible for locating cells within B cell follicles (León et al.,

2012). More recently, interactions between lymphotoxin (LT)-positive B cells and LTβR-positive lymphoid fibroblastic reticular cells (FRCs) have been shown to elicit the formation of new B cell follicles and the relocation of T cells to the follicle mantel and to support antibody production and parasite expulsion (Dubey et al., 2016). These studies highlight the ability of helminth infection models to unveil additional pathways regulating the induction of adaptive immunity, which could prove relevant to other pathogens and/or vaccination strategies.

Helminth infection is typically associated with increased numbers of Treg cells, and depletion of Treg cells promotes the chronicity of *Stronglyoides ratti* (Blankenhaus et al., 2011), whereas enhancing Treg cell numbers by using IL-2-anti-IL-2 mAb2 immune complexes results in the accelerated expulsion of *H. polygyrus* (Smith et al., 2016). Remarkably, adult *H. polygyrus* parasites produce a TGF-β mimic that drives the generation of inducible Treg (iTreg) cells (Grainger et al., 2010), and this generation could function to allow parasite chronicity. However, many of these studies indicate that the main function of Treg cells is to prevent excess immunopathology, as shown by evidence that their complete removal after *H. polygyrus* infection results in excessive pro-inflammatory cytokine secretion, the development of "immunological chaos," and a paradoxical increase in parasite burdens (Smith et al., 2016). Thus, Treg cells form a crucial arm of the '"tolerance" mechanisms invoked after helminth infection.

As noted previously, the accumulation of too many parasites in an individual host results in overt morbidity. In contrast to other pathogens, intestinal helminths (with the exception of *Strongyliodes stercoralis*) are not able to replicate within their mammalian hosts. Thus, adaptive mechanisms induced in response to previous infections can limit the total burdens of adult worms present within an individual host by targeting parasites at their tissue-invasive larval stages.

Targeting tissue-invasive larvae necessarily involves effector cells and mediators distinct from the cells and physiological responses that target adult worms residing within vessels or the intestinal lumen. AAMs have emerged as important cells involved in the trapping and killing of *N. brasiliensis* and *H. polygyrus* tissue larvae after re-infection with these parasites, where Arg1 plays a crucial role. In *N. brasiliensis* infection, AAMs express increased Arg1 in response to IL-13 secretion by Th2 cells, ILC2s, or neutrophils, and they trap larvae as they enter the lung (Bouchery et al., 2015; Chen et al., 2014). For *H. polygyrus*, larval trapping occurs within the intestinal submucosa and requires IL-4- and/or IL-13-driven macrophage proliferation together with IgG-mediated induction of Arg1 (Anthony et al., 2006; Esser-von Bieren et al., 2013). Eosinophils, which are a hallmark of helminth infection, are also associated with enhanced resistance against a variety of human and veterinary helminths. *In vitro* studies have revealed the ability of antibody-activated eosinophils to kill a variety of parasites, including *Ascaris suum* (Masure et al., 2013), *Schistosomiasis mansoni* (Gounni et al., 1994), and *Brugia malayi* (Chandrashekar et al., 1990), at the larval stage. *In vivo* studies have provided evidence that these cells also mediate resistance against *L. sigmodontis* (Specht et al., 2006), *T. spirilas* (Huang et al., 2015b), and *N. brasiliensis* (Knott et al., 2007) at the larval stage. However, complicating matters, eosinophils actually protect muscle-encysted larvae in mice that have been given a primary infection with *T. spirilas* (Huang et al., 2015a) and might play a regulatory role by dampening mast cell recruitment and IgE production after *B. malayi* infection (Cadman et al., 2014) or by dampening IgG1 production after *H. polygyrus* infection (Strandmark et al., 2017). These studies indicate a fascinating complexity in the function of eosinophils, and future studies using helminth models will most likely unveil novel insights into this poorly understood cell type.

Many of the described studies employed models in which challenge infections were given after clearance of the adult worms generated during the primary infection. However, persuasive evidence exists for concomitant immunity, a state in which the presence of adult worms provides the host with ongoing resistance to larval stages of the same organism. This has been hypothesized to occur either because the presence of cross-reactive antigens between the adult and larval stages allows the host to attack tissue-resident larval stages or because immune-driven alterations to tissue physiology render the host more resistant to larval invasion (Chandrashekar et al., 1990). The immune mechanisms underlying concomitant immunity are poorly described, but renewed interest in this form of immunity will most likely yield important insights to type-2-cell-mediated immunity.

Although antibodies are not always necessary for resistance against helminths, increasing evidence indicates that they can be potent mediators of resistance in immune animals. As detailed earlier, specific IgG and IgE antibodies can activate macrophages or eosinophils to attack many helminths at their larval stages. Of note, concomitant immunity in individuals living in areas endemic for *Schistosoma* is also associated with high levels of parasite-specific antibodies (Chandrashekar et al., 1990). Lastly, the transfer of parasite-specific antibodies from mothers to their offspring plays an important role in limiting worm numbers in suckling neonates by providing resistance against infective larvae (Appleton and McGregor, 1984; Harris et al., 2006).

These findings provide renewed optimism for the development of vaccines, given that the production of protective antibodies underlies most successful vaccines (Harris, 2011; Hewitson and Maizels, 2014). On this note, a recent study identified parasite-specific antibodies as a potent mediator of protective immunity against *H. polygyrus* in mice vaccinated with excretory-secretory productions from this worm (Hewitson et al., 2015). Surprisingly, however, the mechanisms by which antibodies provided protection differed from those described for natural infection—indicating that further studies will be necessary to enhance vaccine design.

Altered Immune Homeostasis in the Absence of Helminths and the Impact of Helminth Infection on Host Metabolism and the Microbiome

As discussed earlier, neonates exhibit an exaggerated type-2-cell-mediated immune response that promotes adaptation to their new environment outside of the womb. This immune "bias" could be counterbalanced during weaning as a result of microbial colonization, which functions to dampen type-2-cell-mediated immunity. That this is necessary for immune homeostasis is supported by evidence that allergen exposure in

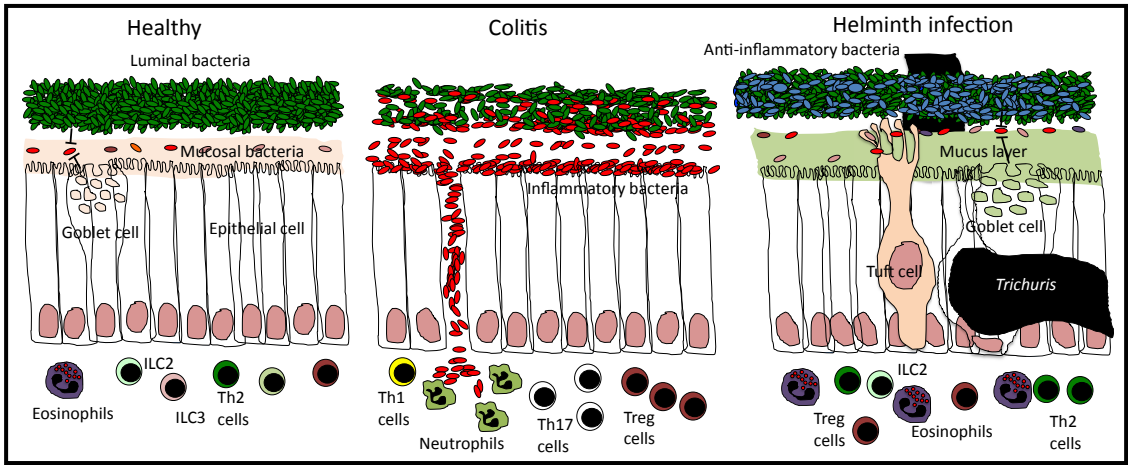

Figure 3. Helminth-Microbiota Interactions

Under steady-state conditions, potentially inflammatory aero-tolerant bacterial pathobionts are found in the mucosa away from the gut lumen, and their expansion is kept in check by the mucous layer, competition with luminal bacteria, and the normal array of intestinal immune cells, including eosinophils, innate lymphoid cells, $CD4^+$ effector T cells, $CD8^+$ effector T cells, and Treg cells. Under conditions of colitis, reduction in the mucous barrier and breaches in the epithelial layer enable the expansion of pathobionts (e.g., *Bacteroides*), which spill into the lumen and cross the epithelial cell layer, where they are kept in check by incoming neutrophils, coordinated by Th17 cells. There is also an increase in Treg cells during gut inflammation to prevent collateral damage. As depicted in Figure 1, helminth colonization elicits type-2-cell-mediated responses involving ILC2s and Th2 cells, all of which are a source of IL-4 and IL-13, as well as IL-22. Eosinophils in the gut are also a potential source of type-2-cell-derived cytokines. These cytokines act on goblet cells to induce increased mucous production, which restores the epithelial barrier and limits the expansion of inflammatory pathobionts. Additionally, these conditions favor the expansion of anti-inflammatory bacteria (e.g., Clostridia), which outcompete the inflammatory pathobionts under these conditions as well as promote the expansion of $CD4^+$ Treg cells through the increased availability of SCFAs. These conditions not only promote the expulsion of the intestinal helminths but also promote tissue repair and the resolution of inflammation directed against gut bacteria, and they can even affect distal tissues, for example, by attenuating allergic inflammation in the airways.

neonates (Gollwitzer et al., 2014) or germ-free mice (Herbst et al., 2011) results in exaggerated type-2-cell-mediated immunity and resulting pathology. Under natural conditions, chronic infection by the environmentally ubiquitous helminths would most likely again reset the homeostatic state to one in which the ongoing production of type-2-cell-mediated immunity and Treg-cell-derived cytokines is tolerated. For example, individuals living in endemic regions and harboring parasites exhibit increased circulating IL-10 and type-2-cell-derived cytokines (Yazdanbakhsh et al., 2002). The mismatch between evolutionary pressures and today's urbanized "helminth-free" societies could partly explain the altered frequency of inflammatory diseases apparent in such populations. Evidence that helminths attenuate allergic and autoimmune disorders can be found in epidemiological and experimental studies and has been linked to multiple factors, including increased Treg cell function, direct immunomodulation by parasitic products, and more recently, helminth-induced modulations to the microbiome (Maizels and McSorley, 2016).

The gut microbiota and intestinal helminths in particular must have co-evolved to occupy the same environmental niche in their mammalian hosts. A molecular understanding of direct interactions between helminths and bacteria is emerging from studies in model organisms such as *C. elegans* (Rangan et al., 2016). However, the host type-2-cell-mediated response also plays a critical role in altering the microbiota after helminth infection by changing the environmental conditions in the gut and favoring certain bacterial communities. Direct evidence that type-2-cell-derived cytokines can alter the gut microbiota during infection with *T. muris* (Ramanan et al., 2016) or *H. polygyrus* (Walk et al., 2010) has been shown in mouse models, but similar shifts have also been observed in human populations (Lee et al., 2014). Helminths that live in the large intestine (e.g., *Trichuris sp.*) might have a bigger impact on the gut microbiota than those living in the small intestine (e.g., *H. polygyrus*, *N. brasiliensis*, and human hookworms) or other tissues (P.L. et al., unpublished data). For *Trichuris* parasites, there is also evidence that the parasites respond to the gut microbiota as part of their life cycle (Hayes et al., 2010), whereby they emerge from their eggs only when encountering specific bacteria in the caecum (Figure 3).

Alterations to the gut microbiota by helminths could contribute toward maintaining intestinal homeostasis and reducing inflammatory responses in the gut. The local type-2-cell-mediated response to helminth infections in the intestine drives goblet cell hyperplasia and epithelial cell turnover, which could restore barrier function and the mucus layer separating IECs from luminal bacteria. These effective resistance mechanisms for expelling parasites might also be important components in maintaining gut integrity. The increased mucus from this response could favor certain bacterial communities, such as the Clostridia (Ramanan et al., 2016), which can induce Treg cells both locally and systemically (Atarashi et al., 2013; Atarashi et al., 2011). One mechanism could be through short-chain fatty acid (SCFA) production, which can have systemic effects including the inhibition of airway inflammation during helminth infection (Zaiss et al., 2015). Another potential mechanism could be competition against inflammatory pathobionts, such as *B. vulgatus* (Ramanan et al., 2014). Colonization resistance promoted by the type-2-cell-mediated response during *T. muris* infection could reduce additional intestinal pathologies in a *Nod2*$^{-/-}$ mouse model of inflammatory bowel disease (Ramanan et al., 2016).

However, there are also potentially detrimental consequences of helminth infections. Host responses to other pathogens, including viral infection (Osborne et al., 2014; Reese et al., 2014) and *Mycobacterium tuberculosis* (Monin et al., 2015; Potian et al., 2011), could be affected. Additionally, there is the possibility of increased tumor formation (Hayes et al., 2017). The cytokine IL-22 is induced by large intestinal helminths (Broadhurst et al., 2010; Turner et al., 2013) and has been shown to promote tumorigenesis in other systems (Huber et al., 2012). Although IL-22 can ameliorate intestinal inflammation (Rutz et al., 2014), it has equally been shown to drive epithelial cell turnover to the point of increasing the emergence of intestinal adenomas (Huber et al., 2012). Because IL-22 affects the composition of gut microbiota, these risks could be associated with the specific communities present in the infected individual.

Most studies so far have focused on the gut microbiota rather than on other tissue sites (e.g., the skin, vagina, lungs, and mouth). Whether systemic type-2-cell-derived cytokine production resulting from helminth infection alters microbial communities in a functionally important manner at other sites remains to be determined. Future studies should also assess the possible contribution of helminth-microbiota interactions to infection-induced changes to host physiology and metabolism.

A landmark study by Wu et al. (2011) utilized *N. brasiliensis* to demonstrate that eosinophils can mediate protection against high-fat diet (HFD)-induced weight gain and insulin resistance by activating AAMs present in white adipose tissue (WAT). This study has sparked a rapidly expanding literature that links type-2-cell-mediated immunity to improved adipose tissue metabolism, also in the steady state (Brestoff and Artis, 2015). A protective role for type-2-cell-mediated immunity in obesity is supported by the finding that obese mice harbor increased CMs, whereas AAMs are more predominant in the WAT of lean mice (Lumeng et al., 2007). Type-2-cell-mediated immune responses reported to regulate WAT metabolic function include IL-4 and/or IL-13 production by eosinophils, iNKT cells, and ILC2s; altered iron storage by AAMs; and ILC2 production of opioid peptides (Brestoff and Artis, 2015). One way in which these mediators exert their function is by promoting the differentiation of "beige" adipocytes, which can participate in thermogenesis (Brestoff and Artis, 2015). Whether helminth infection promotes WAT "beiging" has not been evaluated; however, other studies in mice have supported the initial findings of Wu et al. (2011) by linking helminth infection with resistance against HFD-induced weight gain and/or improved glucose tolerance (Hussaarts et al., 2015; Okada et al., 2013; Wu et al., 2011; Yang et al., 2013). Understanding the impact of helminth infection and type-2-cell-mediated immunity on other metabolic tissues, such as the liver and skeletal muscle, will also be important. In this regard, a recent study using *S. mansoni*-soluble egg antigens demonstrated that type-2-cell-mediated responses elicited in the WAT and liver of treated mice fed a HFD improved both whole-body and organ-specific insulin responsiveness (Hussaarts et al., 2015). Lastly, given that host metabolism is closely linked to the intestinal microbiota, the impact of helminth infection on the microbiome could be of importance.

Helminth infection has also been associated with altered metabolic function in humans and livestock. Emerging evidence in humans indicates a negative association between helminth infection and metabolic syndrome (MetS), a dysregulated metabolic state associated with an increased risk of developing type 2 diabetes and cardiovascular disease. In China, self-reported past infection with *Schistosoma japonicum* is associated with reduced markers of MetS (Shen et al., 2015), and in Indonesia, helminth infection is inversely correlated with body mass index and circulating lipids (Wiria et al., 2013). For livestock, intestinal helminth infection is often associated with reduced nutritional status, typified by protein-losing enteropathy and causing significant agricultural economic losses (Parkins and Holmes, 1989). Both veterinary and experimental studies have reported significant alterations to intestinal physiology, including villus atrophy, mucous secretion, increased intestinal smooth muscle contraction, and altered epithelial cell glucose transport (Parkins and Holmes, 1989; Shea-Donohue et al., 2017). As discussed, many of these responses are driven by the IL-4 and/or IL-13 axis and function to expel adult worms. However, it is also possible that some of these changes contribute to the impact of helminth infection on metabolic status.

Whether helminth-induced alterations to host metabolism have an advantage for the parasite and/or host remains unclear. IL-4 promotes lipolysis—the breakdown of triglycerides into fatty acids (FAs)—in adipocytes (Tsao et al., 2014) and AAMs (Huang et al., 2014). This process could help to nourish the parasite or be necessary to allow the host to use FAs as an alternative energy source as a result of the negative impact of the parasite infection on intestinal glucose uptake. FAs, rather than glucose, are the preferred energy source for AAMs (Huang et al., 2014) and ILC2s (Wilhelm et al., 2016), indicating that lipolysis might also function to "fuel" the protective type-2-cell-mediated immune response. Lastly, it is possible that thermogenesis induced by type-2-cell-mediated immunity functions to counteract the negative impact of helminth infection on host survival over the cold winter period (Gulland, 1992).

Concluding Remarks

Helminth infections remain a significant cause of morbidity worldwide, and understanding the interaction between these organisms and ourselves is essential for developing new strategies for eradication, such as new vaccination approaches. Paradoxically, the elimination of helminths could also alter microbial communities and reset homeostatic mechanisms in complex ways that we should better understand to prevent or treat inflammatory and metabolic diseases that are rapidly increasing in prevalence. For example, why does chronic infection not result in the same pathological processes as allergic inflammation? Can we gain a better understanding of immune regulation, exhaustion, and/or IgE specificities by further characterizing chronic infections? What are the roles of maternal transfer of immunity, the age of acquisition of helminths, and the long-term consequences of early-life exposure to helminths? Given that helminth mouse models have emerged as powerful tools for studying tissue injury and repair via both acute and chronic models of infection, can we build on this understanding to find new ways of driving tissue regeneration without fibrosis? How many more exciting new cellular characters are there to discover after innate lymphocytes, tuft cells, and neurons? Will the many new lessons in mice cross over to our understanding of human immune

responses to helminths, which are different in important ways (for example, the features of macrophage activation and eosinophil function)? Although there has clearly been a newfound interest and appreciation for lessons learned from the complexity of host-helminth interactions by immunologists, we are optimistic that the best days are yet to come and that we will make many more discoveries of the mechanisms governing type-2-cell-mediated immunity by studying our old friends. These in turn will provide new insights into how this arm of the immune system maintains tissue homeostasis.

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