Microbiology Spectrum
American Society for Microbiology Press

Myeloid Cell Phenotypes in Susceptibility and Resistance to Helminth Parasite Infections

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ABSTRACT Many major tropical diseases are caused by long-lived helminth parasites that are able to survive by modulation of the host immune system, including the innate compartment of myeloid cells. In particular, dendritic cells and macrophages show markedly altered phenotypes during parasite infections. In addition, many specialized subsets such as eosinophils and basophils expand dramatically in response to these pathogens. The changes in phenotype and function, and their effects on both immunity to infection and reactivity to bystander antigens such as allergens, are discussed.

INTRODUCTION

The immune system is fundamentally divided into the innate and adaptive arms, predominantly represented by the myeloid and lymphoid lineages, respectively, and largely derived from bone marrow progenitors. This simplistic classification belies an intricate circuitry in which the innate and adaptive cells communicate, stimulate, and regulate each other throughout the course of every immune response. Hence, in every respect myeloid cell populations are instrumental to successful defense against parasitic infections.

Myeloid cells include the heterogeneous monocyte-macrophage lineage, which permeates all tissues of the body, and first emerge as self-renewing progeny of embryonic yolk sac progenitors (1). Subsequent populations of macrophages are derived from the bone marrow (2), as are the closely related dendritic cells (DCs), crucial to initiating immune responses (3); the neutrophils, which are most populous in the circulation; and several other granulocyte subsets (eosinophils, basophils, and mast cells), which expand rapidly in either the bloodstream or tissues during particular parasite infections. In addition, the myeloid cell family includes megakaryocytes, which give rise to platelets in the blood. Each of these cell types is known to play critical roles in one or more parasite infections.

Not surprisingly, parasitic organisms target myeloid cells to divert or block the immune response; some parasitic protozoa, such as *Leishmania* species, *Toxoplasma gondii*, and *Trypanosoma cruzi*, even invade myeloid cells such as neutrophils and macrophages, to survive and propagate in an intracellular lifestyle.

In addition, extracellular parasites such as African trypanosome protozoa and multicellular (metazoan) helminth worms manipulate myeloid cell populations to ensure their survival. The interactions of intracellular parasites with myeloid cells has been dissected and described in fascinating detail (4–7), and hence this review will primarily focus on recent findings implicating the different subsets of myeloid cells in resistance to the metazoan helminth parasites.

Received: 15 July 2016, **Accepted:** 28 September 2016, **Published:** 23 November 2016

Editor: Siamon Gordon, Oxford University, Oxford, United Kingdom

Citation: Maizels RM, Hewitson JP. 2016. Myeloid cell phenotypes in susceptibility and resistance to helminth parasite infections. *Microbiol Spectrum* 4(6):MCHD-0043-2016. doi:10.1128/microbiolspec.MCHD-0043-2016.

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Extracellular parasites cause dramatic alterations in host myeloid cell populations (8, 9). Perhaps the first such observation was of >60% peripheral blood eosinophilia in a patient infected with the nematode *Trichinella spiralis* (10). Eosinophilia is now recognized as an enduring hallmark of helminth infection, although uncertainty remains over the cells' role in eliminating parasites (11, 12). In addition, basophilia is also commonly observed in these infections (13), as is mucosal mast cell hyperplasia in the gut epithelium, where parasites infest the gastrointestinal tract (14).

A more qualitative analysis through molecular markers and gene expression also reveals that each of these myeloid cell types adopts a different phenotype in infections with extracellular parasites, contrasting with the pattern conventionally associated with microbial and intracellular infections. In the case of basophils and eosinophils, this may involve the production of type 2 cytokines such as interleukin-4 (IL-4) (15, 16), while within the macrophage compartment, a distinct profile designated as the alternatively activated macrophage emerges, driven by IL-4 and the related cytokine IL-13 (17). In addition, DCs and neutrophils influenced by the helminth-driven type 2 environment can express gene sets similar to the pattern of alternative activation (18, 19). In this fashion, innate myeloid cells can both set the tone of the adaptive immune response and be instructed by cytokine-producing adaptive cells in the phenotype they adopt. These features will be discussed below for each lineage in turn.

INITIATION OF IMMUNITY: DCs

Helminth infections are the archetypal inducers of the type 2 response, and indeed may have been the selective force that drove the evolution of this mode of immunity (17, 20). The type 2 response begins on a local scale with innate cells (such as innate lymphoid cells) responding to epithelial alarmins (21), but requires the adaptive arm of immunity to gather sufficient strength and attain systemic effects through the differentiation of Th2 cells.

Th2 induction is highly dependent on DCs; for instance, the *in vivo* transfer of bone marrow-derived DCs pulsed with helminth products such as schistosome egg antigen (SEA) (22) or *Nippostrongylus brasiliensis* excretory-secretory antigens (23) is sufficient to stimulate subsequent Th2 differentiation.

Conversely, depletion of $CD11c^+$ DCs *in vivo* greatly impairs Th2 induction in *Schistosoma mansoni* and gut nematode infection (24–26). Despite this, other innate aspects of type 2 immunity, for instance, eosinophilia and alternative macrophage activation, are evoked as normal in a DC-independent manner (26), confirming the unique importance of DCs in recruiting and activating the adaptive immune compartment (27).

DCs represent a heterogeneous set of cells of differing origin and phenotype, suggesting that specialized subsets may be responsible for recognizing and responding to helminth infection. For example, in the dermis, DCs expressing the macrophage galactose-type C-type lectin 2, CD301b, are primarily responding to infection with skin-penetrating larvae of *N. brasiliensis* (28). Conversely, Th2 immunity is elevated in the absence of Batf3-dependent conventional DC (cDC) populations (primarily lymphoid-resident $CD8\alpha^+$ DCs and migratory $CD103^+$ cells), owing to the constitutive production of Th1-promoting IL-12 by these cells (29).

Use of mice with specific defects in particular DC subsets has revealed the importance of interferon regulatory factor 4 (IRF4)-dependent cDC populations, as in animals in which this factor is deleted from the $CD11c^+$ subset, Th2 responses to *N. brasiliensis* are greatly impaired (30). In addition, the Krüppel-like factor KLF4 is also required for normal Th2 responsiveness, and mice lacking this protein within the DCs show poor survival when infected with *S. mansoni* (31). On the other side of the coin, DCs express a surface receptor kinase, Tyro3, that conveys signals that inhibit Th2 induction by the cell; Tyro3-deficient mice mount stronger Th2 responses, clear *N. brasiliensis* more rapidly, and harbor DCs that, when pulsed and transferred into wild-type mice, induce higher levels of type 2 cytokines (32).

In some instances, helminth products can also modulate DCs to drive a stronger regulatory cell component, as *in vitro*, for example, in DC–T-cell cocultures incubated with SEA (33). Similarly, more tolerogenic DCs are induced by coincubation with molecules released by the liver fluke *Fasciola hepatica* (34, 35) and the nematode *T. spiralis* (36, 37). *In vivo*, the immunoregulatory parasite *Heligmosomoides polygyrus* changes the composition of intestinal DCs toward a predominance of $CD11c^{lo}$ cells, which preferentially induce regulatory T cells (Tregs) (25). Interestingly, intestinal DCs from *H. polygyrus*-infected mice could, on transfer into RAG-deficient mice, protect recipients from T-cell-mediated colitis (38). In addition, DCs pulsed with products of the tapeworm *Hymenolepis diminuta* protected recipient mice from pathology in a dinitrobenzene sulfonic acid-induced colitis model (39), and those exposed to *T. spiralis* larval secretions protected from experimental autoimmune encephalitis (40).

Helminth infection also favors DCs adopting an "alternate activation" phenotype (18) akin to that commonly observed in macrophages, and also dependent on IL-4Rα-mediated signaling. In such DCs, there is significant upregulation of Ym1 and resistin-like molecule-α (RELMα) expression, the latter being found to be essential for DC-driven IL-10 production by *in vitro*-polarized Th2 cells.

A major question in the field is how DCs detect the presence of helminth products and discriminate them from microbial organisms to adopt a Th2- (or Treg-) driving program (41). Generally, immune sensing of helminths does not depend on Toll-like receptor (TLR)-mediated interactions and differs from TLR stimulation in key respects. Recognition of SEA by DCs does not upregulate the same pathways of costimulatory surface proteins (e.g., CD40, CD80, and CD86) and inflammatory cytokines (IL-6, IL-12, and tumor necrosis factor) observed when cells encounter a strong TLR ligand such as lipopolysaccharide (LPS) (42). Moreover, some helminth molecules can directly interfere with the response to LPS and other TLR ligands (23, 43–46), raising the question of whether the inability of DCs to fully activate in response to helminths is a host adaptation to this class of parasite or a parasite strategy to dampen host reactivity.

A key component of SEA from schistosome eggs that promotes DC Th2 induction has been identified as a ribonuclease, omega-1, which in native or recombinant form can reproduce the Th2-driving effects of SEA itself (47, 48). Omega-1 is internalized via the mannose receptor, and subsequently degrades RNA within DCs (49), accompanied by cytoskeletal changes within the DC that impair interactions with antigen-specific $CD4^+$ T cells (48). Such low-level DC–T-cell conjugate formation may favor Th2 responses through suboptimal signal delivery. Exposure of DCs to SEA also leads to epigenetic modification crucial for their Th2-polarizing ability, as DCs deficient in methyl-binding protein-2 have altered (predominantly downregulated) gene expression and impaired ability to prime *in vivo* Th2 responses (50).

THE ALTERNATIVELY ACTIVATED MACROPHAGE

Alternatively activated macrophages (AAMs) are those driven through the IL-4/IL-13 type 2 STAT6-dependent pathway, in contrast to cells activated in the classical gamma interferon-dependent manner (51, 52). AAMs are also termed M2 macrophages, in distinction to the classically activated (M1) cells; although inarguably an oversimplification (53), these designations remain useful especially when analyzing *in vivo* macrophage populations in the complex setting of helminth infections.

The AAM phenotype is particularly prominent in parasite infections, having been identified in mice infected with the filarial nematode *Brugia malayi* (54) and subsequently in many other helminth infections (55), as well as in animals infected with the extracellular protozoan parasite *Trypanosoma brucei* (56, 57). In these infections, macrophages present a characteristic pattern of gene expression producing high levels of arginase-1 (Arg-1), RELMα, and the chitinase-like molecule Ym1 (Chi3L3) (58, 59). Macrophage expression of Arg-1 is, for example, essential to inhibit both Th2-mediated liver fibrosis (60) and IL-12/IL-23-dependent gut inflammation in murine schistosomiasis (61). In addition, the metabolism of AAM cells uses oxidative phosphorylation, markedly different from classically activated (M1) macrophages in which the Krebs cycle is interrupted and glycolysis predominates (62).

As discussed above for DCs, helminths and their products are frequently associated with inhibition of the TLR response of macrophages, to the extent that mice infected with the filarial parasite *Litomosoides sigmodontis* show a switch in macrophage phenotype that protects against sepsis during acute bacterial exposure (63).

AAMs may differ from inflammatory M1 macrophages not only in function but also in provenance. Analysis of macrophage populations expanding in the pleural cavity following migration of *L. sigmodontis* showed that stimulation of resident cell division, through IL-4, was the major response to infection (64), in contrast to the M1 inflammatory setting in which circulating monocytes infiltrate into tissue suffering microbial infection. However, this distinction is not absolute and may be either parasite or tissue site specific, since CCR2-dependent monocytes preferentially contribute to the expanded liver AAM population observed in schistosome infection (65, 66). Moreover, while both resident and monocyte-derived macrophages acquired the alternative activation profile in response to IL-4, they differed substantially in transcriptomic profile, and only the blood-derived subset was able to induce FoxP3 expression in T cells (67). Nevertheless, there is ample evidence that macrophages are highly adaptable, acquiring tissue-specific epigenetic marks in response to their environment (68), and are able to adopt similar phenotypes in the tissues irrespective of their anatomical origin (69).

AAMs are of increasing interest also for their physiological roles in homeostasis, repair, and metabolism.

These macrophages are required for wound repair in an acute model of helminth parasite tissue damage caused by migrating larvae of *N. brasiliensis* transiting the lung, which is rapidly resolved in wild-type mice but not in immune-deficient SCID mice (70), or IL-4R-deficient animals unable to generate AAMs (70, 71). In addition, hemorrhage and erythrocyte egress into the bronchoalveolar spaces is controlled by macrophages, as depletion with anti-F4/80 antibody caused blood loss in mice that would otherwise be protected by prior immunization (72).

The combination of anti-inflammatory and repair-promoting functions of AAMs and the ability of helminths to induce this cell type has generated much interest in the potential therapeutic use of macrophages conditioned by helminths or by helminth products (73). So far, investigations have been limited to mouse models, but with promising results including inhibition of colitis with macrophages transferred from schistosome-infected mice (74). Most strikingly, *in vitro* treatment of macrophages with a cysteine protease inhibitor, AvCystatin, induced a strongly regulatory population that was able, on transfer to recipient mice, to suppress both airway allergic inflammation and intestinal colitis (75).

Metabolic dysfunction reflected by insulin resistance and obesity has also been linked to the phenotype of macrophages under the influence of helminth parasites. In *N. brasiliensis* infection, activated eosinophils produced IL-4 that in turn induced AAMs in the adipose tissue, which counteracted obesity and maintained glucose tolerance (16). In another study, SEA, which drives a strong AAM differentiation, was found to reduce atherosclerotic plaque formation in hyperlipidemic mice, with increased IL-10 levels from macrophages (76). Hence, helminth modulation of macrophages can also give rise to beneficial physiological consequences for the host.

The AAM phenotype may become imprinted through epigenetic changes; demethylation at the H3K27 residue of histones associated with the AAM-associated genes Arg-1, RELMα, and Ym1 (Chi3L3) is mediated by the Jmjd3 demethylase enzyme, induced by the IL-4/STAT6 pathway (77). Furthermore, *ex vivo* macrophages recovered from mice exposed to schistosome eggs were found to be demethylated at these loci, providing a physiological backdrop to the findings.

MACROPHAGES AS EFFECTOR CELLS

In recent years, strong evidence has emerged that macrophages are key effectors in the antiparasite response. In *H. polygyrus* infection, depletion of phagocytes through clodronate-loaded liposomes compromised both primary (78) and secondary (79) immunity, while transfer of macrophages (activated by *in vitro* IL-33 treatment) induced clearance of parasites (80). In an *in vivo* chamber implantation model, activated AAMs, but not conventionally activated macrophages, could kill larvae of the nematode *Strongyloides stercoralis* (81), while in the lung, *N. brasiliensis* larvae killing is attenuated in mice depleted of interstitial macrophages with anti-F4/80 antibody (72). Moreover, clearance of adult *N. brasiliensis* is also macrophage dependent, as it is ablated in mice treated with clodronate liposomes (82).

Mechanistically, macrophages may directly trap and attack the helminths (83), release key mediators such as Arg-1 (79), or simply produce necessary cytokines at the site of infection (80). Different parasite species are undoubtedly susceptible or resistant to different pathways of attack, perhaps driving the diversity of mechanisms in play. Some parasites even show a contrary profile, with immunity to the cestode tapeworm *Taenia crassiceps* actually enhanced by AAM depletion (84), reflecting that in this relatively unusual case a type 1 response is protective and is inhibited by the immunosuppressive properties of AAMs.

BASOPHILS—RARE OR WELL DONE?

Basophils are FcεR1$^+$ granulocytes that are scarce in uninfected peripheral blood but expand rapidly following helminth infection through IL-3 and thymic stromal lymphopoietin stimulation (85, 86), and populate tissues such as the liver and lung (87), as well as the skin if ectoparasites such as ticks attempt to feed. Recently several basophil-deficient animal models have been reported, ranging from antibody depletion to lineage ablation, which demonstrate, for example, that immunity to ticks is dependent on IgE-armed basophils (88), probably acting through release of granule contents such as the basophil-specific granzyme mast cell serine protease-8 (MCP-8) (89). Basophil-deficient mice, however, retain the ability to expel primary infections with *N. brasiliensis* but lack the rapid expulsion of secondary challenge infections that occurs in wild-type mice (90). Interestingly, in the case of *H. polygyrus*, basophil-deficient mice are fully competent to clear parasites when immunity is induced by vaccination (91) but in the setting of repeated live infections show impaired clearance of challenge parasites (92).

Controversy has surrounded the role of basophils in induction of the Th2 response. While they are among the first cell types to respond to infection through the

production of IL-4 and were reported to present antigen to naive T cells (93, 94), basophil depletion or ablation does not compromise the generation of Th2 responses *in vivo* to either schistosomes (24) or intestinal nematodes (26, 95, 96). Together with similar data from the house dust mite allergy model (27), a role for basophils in inducing the antigen-specific Th2 response is now effectively excluded. Nevertheless, basophil-derived IL-4 plays an essential role in the skin to induce alternatively activated macrophages (97), and activation of basophils to release IL-4 is itself sufficient to drive a Th2 response (98). Hence the basophil has evolved a critical role in cutaneous defense against ectoparasites while also being an important contributor to the fully developed type 2 response at the systemic level (95).

MAST CELLS

Mast cells are long-lived tissue-resident cells with a characteristic highly granulated morphology associated with both allergic and antiparasite responses (86, 99); like the basophils to which they are closely related, they are promoted by IL-3 but also IL-9 and stem cell factor, for which they carry the c-Kit receptor. Thus, IL-3 administration can accelerate expulsion of the nematode parasite *Strongyloides* (100), although recently this cytokine has also been linked to alternative activation of macrophages (101), clouding interpretation of the data. Likewise, IL-9 promotes both mastocytosis and expulsion of the *T. spiralis* (102), yet is now also known to expand innate lymphoid cells in helminth infection (103).

Historically, many studies were performed with mutants of c-Kit (such as the *W, Wv,* or *Sash* alleles) that lack mast cells, although again more recently it has emerged that innate lymphoid cells also express this receptor. Nevertheless, c-Kit-deficient mice are more susceptible to most helminth parasites that have been reported (reviewed in reference 104), and in the case of *H. polygyrus*, worm burdens are reduced if these mice receive exogenous mast cells (105), arguing that this cell type is a significant component of antiparasite immunity.

EOSINOPHILS

Eosinophilia is the classic corollary of helminth infection, sufficiently so to be an indicative diagnostic feature. While their close association with helminthiases reflects a common pathway for eosinophil activation (through, for example, IL-5 and eotaxin), the part they play is highly dependent on the parasite in question (12). For some helminths, eosinophils fulfill important protective functions, particularly where they intercept tissue-migrating larvae (106). In another example, eosinophils are required to clear the blood-borne first-stage larval microfilariae of *Brugia malayi* (107). However, in schistosomiasis, despite strong evidence for protective effects *in vitro* and in the semipermissive rat model (108), eosinophil-deficient mice show no difference in the course of *S. mansoni* infection compared to their eosinophil-replete counterparts (109).

Studies with IL-5-overexpressing transgenic mice have also indicated that, in sufficient number, eosinophils can kill migrating *N. brasiliensis* larvae (110); notably, larvae from another species, *Toxocara canis*, are unscathed in these mice, perhaps reflecting a long-standing observation that they slough off adhering eosinophils by shedding their surface coat (111). Hence, a picture emerges of this cell type playing very different roles according to the precise nature of the infective parasite.

A further twist is provided by the case of *T. spiralis* infection, in which eosinophils in fact promote infection, with greater killing of parasite larvae in eosinophil-deficient mice, which can be reversed by eosinophil transfer, and which is attributed to their production of IL-10 to block larvicidal nitric oxide production by other innate myeloid cells (12, 112). This instance reiterates the importance of eosinophils as cytokine-producing cells, including IL-4, which, as mentioned above, is key to the activation of AAMs in adipose tissue for glucose homeostasis (16).

NEUTROPHILS

Classically activated neutrophils are the primary defense against bacteria, which they can engulf and degrade through reactive oxygen intermediates; their role in antiparasite responses is much less well defined. Classical studies with neutrophil-depleting antibodies showed impaired immunity to *H. polygyrus*, while parasite burdens were reduced in mice receiving neutrophils from immune mice (113, 114). In an immunization model, neutrophil depletion had no impact on immunity of vaccinated mice, but worm loads in controls undergoing primary infection were significantly higher in the absence of neutrophils (91). Moreover, recently it was found that neutrophil extracellular traps (NETs) form around larvae of *S. stercoralis* in a mouse model system (115), while antibody-mediated neutrophil depletion reduced the ability of immune mice to intercept skin-penetrating larvae of *N. brasiliensis* (72); notably, these effects are partial rather than complete ablation of protection.

In helminth infections, neutrophils may amplify the type 2 response without being the active agents of worm killing. Thus, in *N. brasiliensis* infection, macrophages from parasite-primed animals were able to transfer protection to naive mice, but only if the donor mice had an intact neutrophil population; depletion of neutrophils negated effective priming of macrophages, which was dependent on neutrophil IL-13 production (19).

A further key role for neutrophils was recently elucidated in the *N. brasiliensis* model, in the context of tissue damage in the lung: the chitinase-like product Ym1 stimulated γδ T cells to produce IL-17, which in turn recruited neutrophils; in the lung setting, neutrophils were able to degrade the parasite larvae, compromising their ability to migrate and mature in the gut. At the same time, neutrophils aggravated the injury to the lung, illustrating a complex balance between immunity and pathology with this cell type at the nexus (116).

MYELOID-DERIVED SUPPRESSOR CELLS

An intriguing parallel exists between tumor-associated macrophages as well as the overlapping populations of myeloid-derived suppressor cells (MDSCs; which may present with either a monocytic or a granulocytic phenotype) (117). Such cells inhibit the protective T-cell response to tumors and are largely promoted by STAT3 and STAT6 signals, including IL-4, IL-10, and IL-13; they also characteristically express Arg-1 in a similar manner to AAMs.

In a novel recent study, it was shown that transfer of granulocytic, but not monocytic, MDSCs induced early expulsion of *N. brasiliensis* (118), in a manner that also depended on recipient expression of wild-type c-Kit alleles, while depletion of MDSCs with gemcitabine resulted in greater worm loads in both *N. brasiliensis* and *T. spiralis* infections (119). In contrast, worm burdens in *H. polygyrus*-infected mice actually increased following adoptive transfer of MDSCs due to greater suppression of the Th2 response (120).

TRAINED IMMUNITY AND INNATE "MEMORY"

A consistent and surprising feature of macrophage activation in the lung of *N. brasiliensis*-infected mice is the longevity of the AAM state; although parasites transit the lung for not much more than 24 h, macrophages at the site appear to make a long-term commitment to the AAM phenotype very evident 1 month postinfection (121), which has detrimental consequences as emphysema develops in the lung up to 300 days following the single episode of helminth disruption (122). These prolonged effects in type 2 conditions may be akin to the new concepts of imprinting activation phenotypes of innate myeloid cells following exposure to inflammatory stimuli such as bacterial LPS (123). The parallel is even more striking in that both type 1 "trained immunity" following microbial exposure and type 2 alternative activation are associated with major epigenetic changes to key genomic loci (77, 124).

HOST-PARASITE COEVOLUTION AND THE INNATE IMMUNE SYSTEM

In conclusion, it is interesting to consider how the dialogue between parasites and the myeloid populations may have evolved. Parasites induce major phenotypic changes in host myeloid populations, but the degree to which this is directed by specific parasite products or results from host response mechanisms remains poorly defined. Some parasite mediators, however, have been identified, for example, the cystatins (cysteine protease inhibitors), which block key antigen-processing enzymes (125) as well as cytokine production in macrophages (126) and DCs (127).

More broadly, the diversity of myeloid cell types has clearly evolved to counter the evolution of many classes of pathogens, including protozoa and helminths; with several specialized cells appearing to target helminths in particular, this may reflect the selective pressure to accommodate, regulate, and survive helminth infections that has so strongly shaped the innate immune system that exists today.

ACKNOWLEDGMENT

R.M.M. gratefully acknowledges support through a Wellcome Trust Senior Investigator Award (Ref 106122).

REFERENCES

1. Gomez Perdiguero E, Klapproth K, Schulz C, Busch K, Azzoni E, Crozet L, Garner H, Trouillet C, de Bruijn MF, Geissmann F, Rodewald HR. 2015. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature* **518:**547–551.

2. Bain CC, Hawley CA, Garner H, Scott CL, Schridde A, Steers NJ, Mack M, Joshi A, Guilliams M, Mowat AM, Geissmann F, Jenkins SJ. 2016. Long-lived self-renewing bone marrow-derived macrophages displace embryo-derived cells to inhabit adult serous cavities. *Nat Commun* **7:** ncomms11852. doi:10.1038/ncomms11852.

3. Merad M, Sathe P, Helft J, Miller J, Mortha A. 2013. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annu Rev Immunol* **31:**563–604.

4. Bogdan C. 2008. Mechanisms and consequences of persistence of intracellular pathogens: leishmaniasis as an example. *Cell Microbiol* **10:** 1221–1234.

5. Mashayekhi M, Sandau MM, Dunay IR, Frickel EM, Khan A, Goldszmid RS, Sher A, Ploegh HL, Murphy TL, Sibley LD, Murphy KM. 2011. CD8α$^+$ dendritic cells are the critical source of interleukin-12 that controls acute infection by *Toxoplasma gondii* tachyzoites. *Immunity* **35:**249–259.

6. Ribeiro-Gomes FL, Sacks D. 2012. The influence of early neutrophil-*Leishmania* interactions on the host immune response to infection. *Front Cell Infect Microbiol* **2:**59. doi:10.3389/fcimb.2012.00059.

7. Beattie L, d'El-Rei Hermida M, Moore JW, Maroof A, Brown N, Lagos D, Kaye PM. 2013. A transcriptomic network identified in uninfected macrophages responding to inflammation controls intracellular pathogen survival. *Cell Host Microbe* **14:**357–368.

8. Cadman ET, Lawrence RA. 2010. Granulocytes: effector cells or immunomodulators in the immune response to helminth infection? *Parasite Immunol* **32:**1–19.

9. Barron L, Wynn TA. 2011. Macrophage activation governs schistosomiasis-induced inflammation and fibrosis. *Eur J Immunol* **41:** 2509–2514.

10. Brown TR. 1898. Studies on trichinosis, with especial reference to the increase of the eosinophilic cells in the blood and the muscle, the origin of these cells and their diagnostic importance. *J Exp Med* **3:**315–347.

11. Klion AD, Nutman TB. 2004. The role of eosinophils in host defense against helminth parasites. *J Allergy Clin Immunol* **113:**30–37.

12. Huang L, Appleton JA. 2016. Eosinophils in helminth infection: defenders and dupes. *Trends Parasitol* **32:**798–807.

13. Ohnmacht C, Voehringer D. 2009. Basophil effector function and homeostasis during helminth infection. *Blood* **113:**2816–2825.

14. Miller HR. 1996. Mucosal mast cells and the allergic response against nematode parasites. *Vet Immunol Immunopathol* **54:**331–336.

15. van Panhuys N, Prout M, Forbes E, Min B, Paul WE, Le Gros G. 2011. Basophils are the major producers of IL-4 during primary helminth infection. *J Immunol* **186:**2719–2728.

16. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM. 2011. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* **332:**243–247.

17. Allen JE, Maizels RM. 2011. Diversity and dialogue in immunity to helminths. *Nat Rev Immunol* **11:**375–388.

18. Cook PC, Jones LH, Jenkins SJ, Wynn TA, Allen JE, MacDonald AS. 2012. Alternatively activated dendritic cells regulate CD4$^+$ T-cell polarization in vitro and in vivo. *Proc Natl Acad Sci U S A* **109:**9977–9982.

19. Chen F, Wu W, Millman A, Craft JF, Chen E, Patel N, Boucher JL, Urban JF, Jr, Kim CC, Gause WC. 2014. Neutrophils prime a long-lived effector macrophage phenotype that mediates accelerated helminth expulsion. *Nat Immunol* **15:**938–946.

20. Allen JE, Wynn TA. 2011. Evolution of Th2 immunity: a rapid repair response to tissue destructive pathogens. *PLoS Pathog* **7:**e1002003. doi:10.1371/journal.ppat.1002003.

21. Saenz SA, Taylor BC, Artis D. 2008. Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. *Immunol Rev* **226:**172–190.

22. MacDonald AS, Straw AD, Bauman B, Pearce EJ. 2001. CD8$^-$ dendritic cell activation status plays an integral role in influencing Th2 response development. *J Immunol* **167:**1982–1988.

23. Balic A, Harcus Y, Holland MJ, Maizels RM. 2004. Selective maturation of dendritic cells by *Nippostrongylus brasiliensis*-secreted proteins drives Th2 immune responses. *Eur J Immunol* **34:**3047–3059.

24. Phythian-Adams AT, Cook PC, Lundie RJ, Jones LH, Smith KA, Barr TA, Hochweller K, Anderton SM, Hämmerling GJ, Maizels RM, MacDonald AS. 2010. CD11c depletion severely disrupts Th2 induction and development *in vivo*. *J Exp Med* **207:**2089–2096.

25. Smith KA, Hochweller K, Hämmerling GJ, Boon L, Macdonald AS, Maizels RM. 2011. Chronic helminth infection mediates tolerance in vivo through dominance of CD11c^{lo} CD103$^-$ DC population. *J Immunol* **186:**7098–7109.

26. Smith KA, Harcus Y, Garbi N, Hämmerling GJ, MacDonald AS, Maizels RM. 2012. Type 2 innate immunity in helminth infection is induced redundantly and acts autonomously following CD11c$^+$ cell depletion. *Infect Immun* **80:**3481–3489.

27. Hammad H, Plantinga M, Deswarte K, Pouliot P, Willart MA, Kool M, Muskens F, Lambrecht BN. 2010. Inflammatory dendritic cells—not basophils—are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J Exp Med* **207:**2097–2111.

28. Kumamoto Y, Linehan M, Weinstein JS, Laidlaw BJ, Craft JE, Iwasaki A. 2013. CD301b$^+$ dermal dendritic cells drive T helper 2 cell-mediated immunity. *Immunity* **39:**733–743.

29. Everts B, Tussiwand R, Dreesen L, Fairfax KC, Huang SC, Smith AM, O'Neill CM, Lam WY, Edelson BT, Urban JF, Jr, Murphy KM, Pearce EJ. 2016. Migratory CD103$^+$ dendritic cells suppress helminth-driven type 2 immunity through constitutive expression of IL-12. *J Exp Med* **213:** 35–51.

30. Gao Y, Nish SA, Jiang R, Hou L, Licona-Limón P, Weinstein JS, Zhao H, Medzhitov R. 2013. Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells. *Immunity* **39:**722–732.

31. Tussiwand R, Everts B, Grajales-Reyes GE, Kretzer NM, Iwata A, Bagaitkar J, Wu X, Wong R, Anderson DA, Murphy TL, Pearce EJ, Murphy KM. 2015. *Klf4* expression in conventional dendritic cells is required for T helper 2 cell responses. *Immunity* **42:**916–928.

32. Chan PY, Carrera Silva EA, De Kouchkovsky D, Joannas LD, Hao L, Hu D, Huntsman S, Eng C, Licona-Limón P, Weinstein JS, Herbert DR, Craft JE, Flavell RA, Repetto S, Correale J, Burchard EG, Torgerson DG, Ghosh S, Rothlin CV. 2016. The TAM family receptor tyrosine kinase TYRO3 is a negative regulator of type 2 immunity. *Science* **352:** 99–103.

33. Zaccone P, Burton O, Miller N, Jones FM, Dunne DW, Cooke A. 2009. *Schistosoma mansoni* egg antigens induce Treg that participate in diabetes prevention in NOD mice. *Eur J Immunol* **39:**1098–1107.

34. Dowling DJ, Hamilton CM, Donnelly S, La Course J, Brophy PM, Dalton J, O'Neill SM. 2010. Major secretory antigens of the helminth *Fasciola hepatica* activate a suppressive dendritic cell phenotype that attenuates Th17 cells but fails to activate Th2 immune responses. *Infect Immun* **78:**793–801.

35. Falcón C, Carranza F, Martínez FF, Knubel CP, Masih DT, Motrán CC, Cervi L. 2010. Excretory-secretory products (ESP) from *Fasciola hepatica* induce tolerogenic properties in myeloid dendritic cells. *Vet Immunol Immunopathol* **137:**36–46.

36. Gruden-Movsesijan A, Ilic N, Colic M, Majstorovic I, Vasilev S, Radovic I, Sofronic-Milosavljevic L. 2011. The impact of *Trichinella spiralis* excretory-secretory products on dendritic cells. *Comp Immunol Microbiol Infect Dis* **34:**429–439.

37. Aranzamendi C, Fransen F, Langelaar M, Franssen F, van der Ley P, van Putten JP, Rutten V, Pinelli E. 2012. *Trichinella spiralis*-secreted products modulate DC functionality and expand regulatory T cells *in vitro*. *Parasite Immunol* **34:**210–223.

38. Blum AM, Hang L, Setiawan T, Urban JP, Jr, Stoyanoff KM, Leung J, Weinstock JV. 2012. *Heligmosomoides polygyrus bakeri* induces tolerogenic dendritic cells that block colitis and prevent antigen-specific gut T cell responses. *J Immunol* **189:**2512–2520.

39. Matisz CE, Leung G, Reyes JL, Wang A, Sharkey KA, McKay DM. 2015. Adoptive transfer of helminth antigen-pulsed dendritic cells protects against the development of experimental colitis in mice. *Eur J Immunol* **45:**3126–3139.

40. Sofronic-Milosavljevic LJ, Radovic I, Ilic N, Majstorovic I, Cvetkovic J, Gruden-Movsesijan A. 2013. Application of dendritic cells stimulated with *Trichinella spiralis* excretory-secretory antigens alleviates experimental autoimmune encephalomyelitis. *Med Microbiol Immunol (Berl)* **202:**239–249.

41. Everts B, Smits HH, Hokke CH, Yazdankbakhsh M. 2010. Sensing of helminth infections by dendritic cells via pattern recognition receptors and beyond: consequences for T helper 2 and regulatory T cell polarization. *Eur J Immunol* **40:**1525–1537.

42. Marshall FA, Pearce EJ. 2008. Uncoupling of induced protein processing from maturation in dendritic cells exposed to a highly antigenic preparation from a helminth parasite. *J Immunol* **181:**7562–7570.

43. Cervi L, MacDonald AS, Kane C, Dzierszinski F, Pearce EJ. 2004. Cutting edge: dendritic cells copulsed with microbial and helminth antigens undergo modified maturation, segregate the antigens to distinct intracellular compartments, and concurrently induce microbe-specific Th1 and helminth-specific Th2 responses. *J Immunol* **172:**2016–2020.

44. Segura M, Su Z, Piccirillo C, Stevenson MM. 2007. Impairment of dendritic cell function by excretory-secretory products: a potential mechanism for nematode-induced immunosuppression. *Eur J Immunol* **37:**1887–1904.

45. Langelaar M, Aranzamendi C, Franssen F, Van Der Giessen J, Rutten V, van der Ley P, Pinelli E. 2009. Suppression of dendritic cell maturation by *Trichinella spiralis* excretory/secretory products. *Parasite Immunol* **31:**641–645.

46. Terrazas CA, Alcántara-Hernández M, Bonifaz L, Terrazas LI, Satoskar AR. 2013. Helminth-excreted/secreted products are recognized by multiple receptors on DCs to block the TLR response and bias Th2 polarization in a cRAF dependent pathway. *FASEB J* **27:**4547–4560.

47. Everts B, Perona-Wright G, Smits HH, Hokke CH, van der Ham AJ, Fitzsimmons CM, Doenhoff MJ, van der Bosch J, Mohrs K, Haas H, Mohrs M, Yazdanbakhsh M, Schramm G. 2009. Omega-1, a glycoprotein secreted by *Schistosoma mansoni* eggs, drives Th2 responses. *J Exp Med* **206:**1673–1680.

48. Steinfelder S, Andersen JF, Cannons JL, Feng CG, Joshi M, Dwyer D, Caspar P, Schwartzberg PL, Sher A, Jankovic D. 2009. The major component in schistosome eggs responsible for conditioning dendritic cells for Th2 polarization is a T2 ribonuclease (omega-1). *J Exp Med* **206:**1681–1690.

49. Everts B, Hussaarts L, Driessen NN, Meevissen MH, Schramm G, van der Ham AJ, van der Hoeven B, Scholzen T, Burgdorf S, Mohrs M, Pearce EJ, Hokke CH, Haas H, Smits HH, Yazdanbakhsh M. 2012. Schistosome-derived omega-1 drives Th2 polarization by suppressing protein synthesis following internalization by the mannose receptor. *J Exp Med* **209:**1753–1767, S1.

50. Cook PC, Owen H, Deaton AM, Borger JG, Brown SL, Clouaire T, Jones GR, Jones LH, Lundie RJ, Marley AK, Morrison VL, Phythian-Adams AT, Wachter E, Webb LM, Sutherland TE, Thomas GD, Grainger JR, Selfridge J, McKenzie AN, Allen JE, Fagerholm SC, Maizels RM, Ivens AC, Bird A, MacDonald AS. 2015. A dominant role for the methyl-CpG-binding protein Mbd2 in controlling Th2 induction by dendritic cells. *Nat Commun* **6:**6920. doi:10.1038/ncomms7920.

51. Gordon S. 2003. Alternative activation of macrophages. *Nat Rev Immunol* **3:**23–35.

52. Martinez FO, Helming L, Gordon S. 2009. Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol* **27:**451–483.

53. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, Locati M, Mantovani A, Martinez FO, Mege JL, Mosser DM, Natoli G, Saeij JP, Schultze JL, Shirey KA, Sica A, Suttles J, Udalova I, van Ginderachter JA, Vogel SN, Wynn TA. 2014. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity* **41:**14–20.

54. Allen JE, Lawrence RA, Maizels RM. 1996. Antigen presenting cells from mice harboring the filarial nematode, *Brugia malayi*, prevent cellular proliferation but not cytokine production. *Int Immunol* **8:**143–151.

55. Kreider T, Anthony RM, Urban JF, Jr, Gause WC. 2007. Alternatively activated macrophages in helminth infections. *Curr Opin Immunol* **19:**448–453.

56. Raes G, De Baetselier P, Noël W, Beschin A, Brombacher F, Hassanzadeh Gh G. 2002. Differential expression of FIZZ1 and Ym1 in alternatively versus classically activated macrophages. *J Leukoc Biol* **71:**597–602.

57. Raes G, Beschin A, Ghassabeh GH, De Baetselier P. 2007. Alternatively activated macrophages in protozoan infections. *Curr Opin Immunol* **19:**454–459.

58. Nair MG, Gallagher IJ, Taylor MD, Loke P, Coulson PS, Wilson RA, Maizels RM, Allen JE. 2005. Chitinase and Fizz family members are a generalized feature of nematode infection with selective upregulation of Ym1 and Fizz1 by antigen-presenting cells. *Infect Immun* **73:**385–394.

59. Sutherland TE, Maizels RM, Allen JE. 2009. Chitinases and chitinase-like proteins: potential therapeutic targets for the treatment of T-helper type 2 allergies. *Clin Exp Allergy* **39:**943–955.

60. Pesce JT, Ramalingam TR, Mentink-Kane MM, Wilson MS, El Kasmi KC, Smith AM, Thompson RW, Cheever AW, Murray PJ, Wynn TA. 2009. Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. *PLoS Pathog* **5:**e1000371. doi:10.1371/journal.ppat.1000371.

61. Herbert DR, Orekov T, Roloson A, Ilies M, Perkins C, O'Brien W, Cederbaum S, Christianson DW, Zimmermann N, Rothenberg ME, Finkelman FD. 2010. Arginase I suppresses IL-12/IL-23p40-driven intestinal inflammation during acute schistosomiasis. *J Immunol* **184:**6438–6446.

62. O'Neill LA, Pearce EJ. 2016. Immunometabolism governs dendritic cell and macrophage function. *J Exp Med* **213:**15–23.

63. Gondorf F, Berbudi A, Buerfent BC, Ajendra J, Bloemker D, Specht S, Schmidt D, Neumann AL, Layland LE, Hoerauf A, Hübner MP. 2015. Chronic filarial infection provides protection against bacterial sepsis by functionally reprogramming macrophages. *PLoS Pathog* **11:**e1004616. doi:10.1371/journal.ppat.1004616.

64. Jenkins SJ, Ruckerl D, Cook PC, Jones LH, Finkelman FD, van Rooijen N, MacDonald AS, Allen JE. 2011. Local macrophage proliferation, rather than recruitment from the blood, is a signature of T_H2 inflammation. *Science* **332:**1284–1288.

65. Girgis NM, Gundra UM, Ward LN, Cabrera M, Frevert U, Loke P. 2014. $Ly6C^{high}$ monocytes become alternatively activated macrophages in schistosome granulomas with help from $CD4^+$ cells. *PLoS Pathog* **10:**e1004080. doi:10.1371/journal.ppat.1004080.

66. Nascimento M, Huang SC, Smith A, Everts B, Lam W, Bassity E, Gautier EL, Randolph GJ, Pearce EJ. 2014. $Ly6C^{hi}$ monocyte recruitment is responsible for Th2 associated host-protective macrophage accumulation in liver inflammation due to schistosomiasis. *PLoS Pathog* **10:**e1004282. doi:10.1371/journal.ppat.1004282.

67. Gundra UM, Girgis NM, Ruckerl D, Jenkins S, Ward LN, Kurtz ZD, Wiens KE, Tang MS, Basu-Roy U, Mansukhani A, Allen JE, Loke P. 2014. Alternatively activated macrophages derived from monocytes and tissue macrophages are phenotypically and functionally distinct. *Blood* **123:**e110–e122. doi:10.1182/blood-2013-08-520619.

68. Lavin Y, Winter D, Blecher-Gonen R, David E, Keren-Shaul H, Merad M, Jung S, Amit I. 2014. Tissue-resident macrophage enhancer landscapes are shaped by the local microenvironment. *Cell* **159:**1312–1326.

69. van de Laar L, Saelens W, De Prijck S, Martens L, Scott CL, Van Isterdael G, Hoffmann E, Beyaert R, Saeys Y, Lambrecht BN, Guilliams M. 2016. Yolk sac macrophages, fetal liver, and adult monocytes can colonize an empty niche and develop into functional tissue-resident macrophages. *Immunity* **44:**755–768.

70. Reece JJ, Siracusa MC, Scott AL. 2006. Innate immune responses to lung-stage helminth infection induce alternatively activated alveolar macrophages. *Infect Immun* **74:**4970–4981.

71. Chen F, Liu Z, Wu W, Rozo C, Bowdridge S, Millman A, Van Rooijen N, Urban JF, Jr, Wynn TA, Gause WC. 2012. An essential role for T_H2-

type responses in limiting acute tissue damage during experimental helminth infection. *Nat Med* **18:**260–266.

72. Bouchery T, Kyle R, Camberis M, Shepherd A, Filbey K, Smith A, Harvie M, Painter G, Johnston K, Ferguson P, Jain R, Roediger B, Delahunt B, Weninger W, Forbes-Blom E, Le Gros G. 2015. ILC2s and T cells cooperate to ensure maintenance of M2 macrophages for lung immunity against hookworms. *Nat Commun* **6:**6970. doi:10.1038/ncomms7970.

73. Steinfelder S, O'Regan NL, Hartmann S. 2016. Diplomatic assistance: can helminth-modulated macrophages act as treatment for inflammatory disease? *PLoS Pathog* **12:**e1005480. doi:10.1371/journal.ppat.1005480.

74. Smith P, Mangan NE, Walsh CM, Fallon RE, McKenzie AN, van Rooijen N, Fallon PG. 2007. Infection with a helminth parasite prevents experimental colitis via a macrophage-mediated mechanism. *J Immunol* **178:**4557–4566.

75. Ziegler T, Rausch S, Steinfelder S, Klotz C, Hepworth MR, Kühl AA, Burda PC, Lucius R, Hartmann S. 2015. A novel regulatory macrophage induced by a helminth molecule instructs IL-10 in $CD4^+$ T cells and protects against mucosal inflammation. *J Immunol* **194:**1555–1564.

76. Wolfs IM, Stöger JL, Goossens P, Pöttgens C, Gijbels MJ, Wijnands E, van der Vorst EP, van Gorp P, Beckers L, Engel D, Biessen EA, Kraal G, van Die I, Donners MM, de Winther MP. 2014. Reprogramming macrophages to an anti-inflammatory phenotype by helminth antigens reduces murine atherosclerosis. *FASEB J* **28:**288–299.

77. Ishii M, Wen H, Corsa CA, Liu T, Coelho AL, Allen RM, Carson WF IV, Cavassani KA, Li X, Lukacs NW, Hogaboam CM, Dou Y, Kunkel SL. 2009. Epigenetic regulation of the alternatively activated macrophage phenotype. *Blood* **114:**3244–3254.

78. Filbey KJ, Grainger JR, Smith KA, Boon L, van Rooijen N, Harcus Y, Jenkins S, Hewitson JP, Maizels RM. 2014. Innate and adaptive type 2 immune cell responses in genetically controlled resistance to intestinal helminth infection. *Immunol Cell Biol* **92:**436–448.

79. Anthony RM, Urban JF, Jr, Alem F, Hamed HA, Rozo CT, Boucher JL, Van Rooijen N, Gause WC. 2006. Memory T_H2 cells induce alternatively activated macrophages to mediate protection against nematode parasites. *Nat Med* **12:**955–960.

80. Yang Z, Grinchuk V, Urban JF, Jr, Bohl J, Sun R, Notari L, Yan S, Ramalingam T, Keegan AD, Wynn TA, Shea-Donohue T, Zhao A. 2013. Macrophages as IL-25/IL-33-responsive cells play an important role in the induction of type 2 immunity. *PLoS One* **8:**e59441. doi:10.1371/journal.pone.0059441.

81. Bonne-Année S, Kerepesi LA, Hess JA, O'Connell AE, Lok JB, Nolan TJ, Abraham D. 2013. Human and mouse macrophages collaborate with neutrophils to kill larval *Strongyloides stercoralis*. *Infect Immun* **81:**3346–3355.

82. Zhao A, Urban JF, Jr, Anthony RM, Sun R, Stiltz J, van Rooijen N, Wynn TA, Gause WC, Shea-Donohue T. 2008. Th2 cytokine-induced alterations in intestinal smooth muscle function depend on alternatively activated macrophages. *Gastroenterology* **135:**217–225.e1. doi:10.1053/j.gastro.2008.03.077.

83. Esser-von Bieren J, Volpe B, Kulagin M, Sutherland DB, Guiet R, Seitz A, Marsland BJ, Verbeek JS, Harris NL. 2015. Antibody-mediated trapping of helminth larvae requires CD11b and Fcγ receptor I. *J Immunol* **194:**1154–1163.

84. Reyes JL, Terrazas CA, Alonso-Trujillo J, van Rooijen N, Satoskar AR, Terrazas LI. 2010. Early removal of alternatively activated macrophages leads to *Taenia crassiceps* cysticercosis clearance in vivo. *Int J Parasitol* **40:**731–742.

85. Sullivan BM, Locksley RM. 2009. Basophils: a nonredundant contributor to host immunity. *Immunity* **30:**12–20.

86. Voehringer D. 2013. Protective and pathological roles of mast cells and basophils. *Nat Rev Immunol* **13:**362–375.

87. Min B, Prout M, Hu-Li J, Zhu J, Jankovic D, Morgan ES, Urban JF, Jr, Dvorak AM, Finkelman FD, LeGros G, Paul WE. 2004. Basophils produce IL-4 and accumulate in tissues after infection with a Th2-inducing parasite. *J Exp Med* **200:**507–517.

88. Wada T, Ishiwata K, Koseki H, Ishikura T, Ugajin T, Ohnuma N, Obata K, Ishikawa R, Yoshikawa S, Mukai K, Kawano Y, Minegishi Y, Yokozeki H, Watanabe N, Karasuyama H. 2010. Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. *J Clin Invest* **120:**2867–2875.

89. Karasuyama H, Mukai K, Obata K, Tsujimura Y, Wada T. 2011. Nonredundant roles of basophils in immunity. *Annu Rev Immunol* **29:**45–69.

90. Ohnmacht C, Schwartz C, Panzer M, Schiedewitz I, Naumann R, Voehringer D. 2010. Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths. *Immunity* **33:**364–374.

91. Hewitson JP, Filbey KJ, Esser-von Bieren J, Camberis M, Schwartz C, Murray J, Reynolds LA, Blair N, Robertson E, Harcus Y, Boon L, Huang SC, Yang L, Tu Y, Miller MJ, Voehringer D, Le Gros G, Harris N, Maizels RM. 2015. Concerted activity of IgG1 antibodies and IL-4/IL-25-dependent effector cells trap helminth larvae in the tissues following vaccination with defined secreted antigens, providing sterile immunity to challenge infection. *PLoS Pathog* **11:**e1004676. doi:10.1371/journal.ppat.1004676.

92. Schwartz C, Turqueti-Neves A, Hartmann S, Yu P, Nimmerjahn F, Voehringer D. 2014. Basophil-mediated protection against gastrointestinal helminths requires IgE-induced cytokine secretion. *Proc Natl Acad Sci U S A* **111:**E5169–E5177. doi:10.1073/pnas.1412663111.

93. Perrigoue JG, Saenz SA, Siracusa MC, Allenspach EJ, Taylor BC, Giacomin PR, Nair MG, Du Y, Zaph C, van Rooijen N, Comeau MR, Pearce EJ, Laufer TM, Artis D. 2009. MHC class II-dependent basophil-$CD4^+$ T cell interactions promote T_H2 cytokine-dependent immunity. *Nat Immunol* **10:**697–705.

94. Sokol CL, Chu NQ, Yu S, Nish SA, Laufer TM, Medzhitov R. 2009. Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. *Nat Immunol* **10:**713–720.

95. Sullivan BM, Liang HE, Bando JK, Wu D, Cheng LE, McKerrow JK, Allen CD, Locksley RM. 2011. Genetic analysis of basophil function *in vivo*. *Nat Immunol* **12:**527–535.

96. Kim S, Prout M, Ramshaw H, Lopez AF, LeGros G, Min B. 2010. Cutting edge: basophils are transiently recruited into the draining lymph nodes during helminth infection via IL-3, but infection-induced Th2 immunity can develop without basophil lymph node recruitment or IL-3. *J Immunol* **184:**1143–1147.

97. Egawa M, Mukai K, Yoshikawa S, Iki M, Mukaida N, Kawano Y, Minegishi Y, Karasuyama H. 2013. Inflammatory monocytes recruited to allergic skin acquire an anti-inflammatory M2 phenotype via basophil-derived interleukin-4. *Immunity* **38:**570–580.

98. Khodoun MV, Orekhova T, Potter C, Morris S, Finkelman FD. 2004. Basophils initiate IL-4 production during a memory T-dependent response. *J Exp Med* **200:**857–870.

99. Abraham SN, St John AL. 2010. Mast cell-orchestrated immunity to pathogens. *Nat Rev Immunol* **10:**440–452.

100. Abe T, Nawa Y. 1988. Worm expulsion and mucosal mast cell response induced by repetitive IL-3 administration in *Strongyloides ratti*-infected nude mice. *Immunology* **63:**181–185.

101. Borriello F, Longo M, Spinelli R, Pecoraro A, Granata F, Staiano RI, Loffredo S, Spadaro G, Beguinot F, Schroeder J, Marone G. 2015. IL-3 synergises with basophil-derived IL-4 and IL-13 to promote the alternative activation of human monocytes. *Eur J Immunol* **45:**2042–2051.

102. Faulkner H, Humphreys N, Renauld J-C, Van Snick J, Grencis R. 1997. Interleukin-9 is involved in host protective immunity to intestinal nematode infection. *Eur J Immunol* **27:**2536–2540.

103. Turner J-E, Morrison PJ, Wilhelm C, Wilson M, Ahlfors H, Renauld J-C, Panzer U, Helmby H, Stockinger B. 2013. IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med* **210:**2951–2965.

104. Reber LL, Sibilano R, Mukai K, Galli SJ. 2015. Potential effector and immunoregulatory functions of mast cells in mucosal immunity. *Mucosal Immunol* **8:**444–463.

105. Hepworth MR, Daniłowicz-Luebert E, Rausch S, Metz M, Klotz C, Maurer M, Hartmann S. 2012. Mast cells orchestrate type 2 immunity to helminths through regulation of tissue-derived cytokines. *Proc Natl Acad Sci U S A* **109:**6644–6649.

106. Huang L, Gebreselassie NG, Gagliardo LF, Ruyechan MC, Luber KL, Lee NA, Lee JJ, Appleton JA. 2015. Eosinophils mediate protective immunity against secondary nematode infection. *J Immunol* **194:**283–290.

107. Cadman ET, Thysse KA, Bearder S, Cheung AY, Johnston AC, Lee JJ, Lawrence RA. 2014. Eosinophils are important for protection, immunoregulation and pathology during infection with nematode microfilariae. *PLoS Pathog* **10:**e1003988. doi:10.1371/journal.ppat.1003988.

108. Capron M, Capron A. 1992. Effector functions of eosinophils in schistosomiasis. *Mem Inst Oswaldo Cruz* **87**(Suppl 4)**:**167–170.

109. Swartz JM, Dyer KD, Cheever AW, Ramalingam T, Pesnicak L, Domachowske JB, Lee JJ, Lee NA, Foster PS, Wynn TA, Rosenberg HF. 2006. *Schistosoma mansoni* infection in eosinophil lineage-ablated mice. *Blood* **108:**2420–2427.

110. Dent LA, Daly CM, Mayrhofer G, Zimmerman T, Hallett A, Bignold LP, Creaney J, Parsons JC. 1999. Interleukin-5 transgenic mice show enhanced resistance to primary infections with *Nippostrongylus brasiliensis* but not primary infections with *Toxocara canis*. *Infect Immun* **67:**989–993.

111. Fattah DI, Maizels RM, McLaren DJ, Spry CJ. 1986. *Toxocara canis*: interaction of human blood eosinophils with the infective larvae. *Exp Parasitol* **61:**421–431.

112. Gebreselassie NG, Moorhead AR, Fabre V, Gagliardo LF, Lee NA, Lee JJ, Appleton JA. 2012. Eosinophils preserve parasitic nematode larvae by regulating local immunity. *J Immunol* **188:**417–425.

113. Penttila IA, Ey PL, Jenkin CR. 1984. Infection of mice with *Nematospiroides dubius*: demonstration of neutrophil-mediated immunity *in vivo* in the presence of antibodies. *Immunology* **53:**147–154.

114. Penttila IA, Ey PL, Jenkin CR. 1984. Reduced infectivity of *Nematospiroides dubius* larvae after incubation *in vitro* with neutrophils or eosinophils from infected mice and a lack of effect by neutrophils from normal mice. *Parasite Immunol* **6:**295–308.

115. Bonne-Année S, Kerepesi LA, Hess JA, Wesolowski J, Paumet F, Lok JB, Nolan TJ, Abraham D. 2014. Extracellular traps are associated with human and mouse neutrophil and macrophage mediated killing of larval *Strongyloides stercoralis*. *Microbes Infect* **16:**502–511.

116. Sutherland TE, Logan N, Rückerl D, Humbles AA, Allan SM, Papayannopoulos V, Stockinger B, Maizels RM, Allen JE. 2014. Chitinase-like proteins promote IL-17-mediated neutrophilia in a tradeoff between nematode killing and host damage. *Nat Immunol* **15:**1116–1125.

117. Van Ginderachter JA, Beschin A, De Baetselier P, Raes G. 2010. Myeloid-derived suppressor cells in parasitic infections. *Eur J Immunol* **40:**2976–2985.

118. Saleem SJ, Martin RK, Morales JK, Sturgill JL, Gibb DR, Graham L, Bear HD, Manjili MH, Ryan JJ, Conrad DH. 2012. Cutting edge: mast cells critically augment myeloid-derived suppressor cell activity. *J Immunol* **189:**511–515.

119. Morales JK, Saleem SJ, Martin RK, Saunders BL, Barnstein BO, Faber TW, Pullen NA, Kolawole EM, Brooks KB, Norton SK, Sturgill J, Graham L, Bear HD, Urban JF, Jr, Lantz CS, Conrad DH, Ryan JJ. 2014. Myeloid-derived suppressor cells enhance IgE-mediated mast cell responses. *J Leukoc Biol* **95:**643–650.

120. Valanparambil RM, Tam M, Jardim A, Geary TG, Stevenson MM. 2016. Primary *Heligmosomoides polygyrus bakeri* infection induces myeloid-derived suppressor cells that suppress CD4$^+$ Th2 responses and promote chronic infection. *Mucosal Immunol* doi:10.1038/mi.2016.36.

121. Reece JJ, Siracusa MC, Southard TL, Brayton CF, Urban JF, Jr, Scott AL. 2008. Hookworm-induced persistent changes to the immunological environment of the lung. *Infect Immun* **76:**3511–3524.

122. Marsland BJ, Kurrer M, Reissmann R, Harris NL, Kopf M. 2008. *Nippostrongylus brasiliensis* infection leads to the development of emphysema associated with the induction of alternatively activated macrophages. *Eur J Immunol* **38:**479–488.

123. Netea MG, Quintin J, van der Meer JW. 2011. Trained immunity: a memory for innate host defense. *Cell Host Microbe* **9:**355–361.

124. Saeed S, Quintin J, Kerstens HH, Rao NA, Aghajanirefah A, Matarese F, Cheng SC, Ratter J, Berentsen K, van der Ent MA, Sharifi N, Janssen-Megens EM, Ter Huurne M, Mandoli A, van Schaik T, Ng A, Burden F, Downes K, Frontini M, Kumar V, Giamarellos-Bourboulis EJ, Ouwehand WH, van der Meer JW, Joosten LA, Wijmenga C, Martens JH, Xavier RJ, Logie C, Netea MG, Stunnenberg HG. 2014. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science* **345:**1251086. doi:10.1126/science.1251086.

125. Manoury B, Gregory WF, Maizels RM, Watts C. 2001. *Bm*-CPI-2, a cystatin homolog secreted by the filarial parasite *Brugia malayi*, inhibits class II MHC-restricted antigen processing. *Curr Biol* **11:**447–451.

126. Klotz C, Ziegler T, Figueiredo AS, Rausch S, Hepworth MR, Obsivac N, Sers C, Lang R, Hammerstein P, Lucius R, Hartmann S. 2011. A helminth immunomodulator exploits host signaling events to regulate cytokine production in macrophages. *PLoS Pathog* **7:**e1001248. doi:10.1371/journal.ppat.1001248.

127. Sun Y, Liu G, Li Z, Chen Y, Liu Y, Liu B, Su Z. 2012. Modulation of dendritic cell function and immune response by cysteine protease inhibitor from murine nematode parasite *Heligmosomoides polygyrus*. *Immunology* **138:**370–381.