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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.

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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 CD8α⁺ 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-4R α -mediated signaling. In such DCs, there is significant upregulation of Ym1 and resistin-like molecule- α (RELM α) 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), RELM α , 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 broncho-alveolar 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, RELM α , 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 Fc ϵ R1⁺ 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*, *W^v*, 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 helminthiasis 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 $\gamma\delta$ 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 emphy-

sema 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.

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