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Alternatively activated macrophages in helminth infections

Timothy Kreider¹, Robert M. Anthony², Joseph F. Urban Jr.³, and William C. Gause^{1,*}

¹ Department of Medicine, UMDNJ – New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103; kreideti@umdnj.edu, gausewc@umdnj.edu.

² The Laboratory of Molecular Genetics and Immunology, The Rockefeller University, 1230 York Avenue, New York, NY 10021; ranthony01@mail.rockefeller.edu.

³ Nutrient Requirements and Functions Laboratory, Beltsville Human Nutrition Research Center, US Department of Agriculture, 10300 Baltimore Avenue, Bldg 307-C BARC-East, Beltsville, MD 20705; joe.urban@ars.usda.gov.

Summary

Helminthic parasites can trigger highly polarized immune responses typically associated with increased numbers of CD4⁺ Th2 cells, eosinophils, mast cells, and basophils. These cell populations are thought to coordinate an effective response ultimately leading to parasite expulsion, but they also play a role in the regulation of associated pathologic inflammation. Recent studies suggest that macrophages, conventionally associated with IFN γ -dominant Th1-type responses to many bacteria and viruses, also play an essential role in the Th2-type inflammatory response. These macrophages are referred to as alternatively activated macrophages (AAM Φ s) as they express a characteristic pattern of cell surface and secreted molecules distinct from that of classically activated macrophages (CAM Φ s) associated with microbe infections. In this review, we will discuss recent findings

*Corresponding author

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Annotations

** Anthony, 2006 [3]

This work demonstrated a direct role for AAM Φ s in protection. Clearance of *H. polygyrus* by the Th2-type memory response was abrogated by selective macrophage depletion with clodronate liposomes or by prevention of AAM Φ function with an arginase-1 inhibitor.

* Nair, 2005 [10]

The authors show that AAM Φ expression of ChAFFs is common to the site of infection of *B. malayi*, *L. sigmodontis*, and *N. brasiliensis*.

* Gratchev, 2005 [14]

The authors demonstrated *in vitro* that AAM Φ s express several factors involved in wound repair and that glucocorticoids inhibited this expression.

* Pesce, 2006 [20]

This study established IL-21 as a key cytokine in the AAM Φ response to helminths. Signs of the Th2-type response to *N. brasiliensis* and *S. mansoni*, including markers of AAM Φ s, were reduced in IL-21R α ^{−/−} mice. *In vitro*, IL-21 upregulated IL-4R α and IL-13R α 1 expression on macrophages, thereby enhancing AAM Φ polarization.

* Taylor, 2006 [23]

Suppression of CD4⁺ T cells by AAM Φ s at the site of *L. sigmodontis* infection was independent of IL-10 and CTLA-4 and partly dependent on TGF- β .

* Rodriguez-Sosa, 2006 [24]

Co-infection with *T. crassiceps* lead to increased susceptibility to the intracellular parasite *Leishmania*. AAM Φ s were induced by the cestode despite abundant IFN- γ produced by the Th1-type response to *Leishmania*.

* Reese, 2007 [25]

In vivo administration of chitin resulted in activation of AAM Φ s, which subsequently recruited eosinophils via leukotriene B₄.

* Voehringer, 2007 [45]

Selective depletion of macrophages by clodronate liposomes or their absence in *op/op* mice lead to reduced eosinophil recruitment to the lungs during *N. brasiliensis* infection, as did STAT6-deficiency in non-eosinophil hematopoietic cells. Together these results suggest that AAM Φ s play a role in eosinophilia at the site of nematode infection.

regarding the role of AAMΦs in the development of disease and host protection following helminth infection.

Introduction

Helminths comprise a variety of parasitic worms, including intestinal and filarial nematodes, cestodes and trematodes. Although each triggers characteristic infections associated with the biology of the specific parasite, they all evoke immune responses that share common features. These immune responses typically include elevations in Th2 cytokines: IL-4, IL-5, IL-9, IL-13, and, more recently, IL-21 and IL-25 (IL-17E), which may actually be produced by a Th25 population [1]. The consequent immune response includes polarization of T-helper cells to Th2 cells, eosinophilia, basophilia, mastocytosis, and elevations in serum IgE and IgG1. Most recently, macrophages activated during Th2-type responses have been extensively studied and have been shown to exhibit a very different phenotype from the classically activated macrophages (CAMΦs) stimulated during Th1-type responses: hence the name alternatively activated macrophages (AAMΦs). In this review we will briefly discuss recent insights into the mechanisms of AAMΦ activation and function in the context of helminth infection using experimental mouse models.

Characterization and phenotype

AAMΦs are observed in a variety of helminth infections, including Th2-type immune responses to *Schistosoma mansoni* [2], *Heligmosomoides polygyrus* [3], *Nippostrongylus brasiliensis* [4], *Taenia crassiceps* [5], *Trichinella spiralis* [6], *Fasciola hepatica* [7], *Ascaris suum* [8], and filarial parasites [9]. A number of markers are used to identify AAMΦs (Figure 1). Cell surface IL-4Rα and the mannose receptor (CD206), are readily detected using either flow cytometric [2] or immunohistologic [3] techniques. Arginase-1 is upregulated in AAMΦs and, due to its higher affinity for arginine, out-competes inducible nitric oxide synthase (iNOS), which metabolizes arginine in CAMΦs. Therefore arginase-1 and its metabolic products, including urea and proline, are also indicative of AAMΦ differentiation. AAMΦs express certain chitinase and FIZZ (found in inflammatory zone) family member proteins (ChAFFs), including: FIZZ1/RELMA, Ym1, and acidic mammalian chitinase (AMCase) [10]; the Ym1 transcript shows the highest upregulation of any gene in AAMΦs during nematode infection [11]. Other recently described moieties on AAMΦs include: mouse macrophage galactose-type C-type lectins (mMGL1, mMGL2) [12], WSX-1 (IL-27Rα) [13], matrix metalloproteinases (MMPs) and extracellular matrix protein βIG-H3 [14].

Alternative activation of macrophages

AAMΦs have been classified as a subset of M2 macrophages, which are activated macrophages distinguished by their low expression levels of IL-12 [15]. M2 macrophages can be divided into three groups distinguished by activation factors *in vitro*: IL-4 or IL-13 (M2a or AAMΦ), IL-10 or glucocorticoids (M2b), or immune complexes plus Toll-like receptor ligands (M2c). Macrophages show distinct and non-overlapping gene expression patterns when stimulated by IL-14/IL-13 versus IL-10 [16], though M2a and M2b are generally anti-inflammatory. Recent studies suggest that M2c, despite expressing high levels of IL-10, may actually be more similar to CAMΦs than to the other M2 subsets [17]. Also, an intriguing myeloid suppressor cell (MSC) population expressing F4/80, CD11b, and Gr-1 has been identified in *S. mansoni* [18] and *Taenia crassiceps* [19] infection as suppressing Th1-type responses. However, the AAMΦ population, stimulated by IL-4 and IL-13, is the best characterized in responses to helminths, and thus will be emphasized in this review. The newly identified Th2 cytokine, IL-21, also appears to augment alternative macrophage activation. IL-21R^{-/-} mice infected with *N. brasiliensis*, *H. polygyrus*, or *S. mansoni* have an attenuated Th2-type response with little effect

on IFN- γ production, demonstrating that IL-21R signaling augments the Th2 cell response [20,21]. Increases in Ym1, AMCase, and FIZZ1/RELM α expression also required IL-21R interactions, suggesting that IL-21 promotes AAM Φ polarization, with *in vitro* studies suggesting that IL-21 interactions augment macrophage responsiveness to IL-4 and IL-13 [20]. Another cytokine with a possible role in directly or indirectly activating AAM Φ s is thymic stromal lymphopoietin (TSLP), which polarizes dendritic cells and T cells to a Th2 phenotype [22].

In murine models of filarial infection, nematode-elicited macrophages (NeM Φ s) express a phenotype characteristic of AAM Φ s. NeM Φ s recruited to the peritoneum following implantation of *Brugia malayi* adult worms express arginase-1, Ym1, and FIZZ1/RELM α [10]. Similarly, recent studies of *Litomosoides sigmodontis* infection showed recruitment of arginase-1-expressing F4/80⁺ macrophages [23]. In the strictly enteric *H. polygyrus* infection, during memory, but not primary, responses, AAM Φ s accumulate at sites of larval invasion in the submucosa as early as four days after inoculation. Adoptive transfer experiments of memory CD4⁺ T cells into STAT6-deficient or WT mice given a primary *H. polygyrus* inoculation indicated that IL-4R signaling on macrophages mediated their alternative activation, and suggested that IL-4/IL-13 production by memory CD4⁺ T cells induced AAM Φ recruitment and differentiation at the host:parasite interface [3]. In contrast, rapid increases of AAM Φ s are detected in the lung by 4 days after *N. brasiliensis* infection in SCID mice lacking T cells, and this increase is associated with elevated Ym1, FIZZ1/RELM α , and arginase-1. After day 4, however, expression of these genes decreases markedly in the lungs of *N. brasiliensis*-infected SCID but not in infected WT mice [4], suggesting that innate cells may make sufficient IL-4/IL-13 to induce initial differentiation of AAM Φ s, but that Th2 cells are required to sustain their activity. Mice infected with the cestode *T. crassiceps* and subsequently co-infected with either of two protozoan species of *Leishmania* exhibit a potent Th2-type response without downregulating IFN- γ levels; nevertheless, the protective response to *Leishmania* is blocked and disease exacerbated. AAM Φ s develop in this environment, as sorted macrophages express mRNA transcripts for arginase-1, Ym1, and CD206 [24]. These findings suggest that *T. crassiceps* can induce IL-4 production and the induction of AAM Φ s that are not appropriate for control of *Leishmania* even in the context of a developing Th1-type response. The trematode *F. hepatica* induces an IL-4-dependent Th2-type response, and recent studies indicate that AAM Φ s are recruited to the peritoneal cavity by 24 hours after infection; this response can be replicated with intraperitoneal injection of thioredoxin peroxidase, an excretory/secretory (ES) product of *F. hepatica*. Furthermore, *in vitro* cultures of this parasite product with RAW 264.7 macrophages showed differentiation to an AAM Φ phenotype [7]. The importance of IL-4R signaling in AAM Φ development during helminth infection is underscored by studies of mice lacking IL-4R α expression selectively in macrophages. In these LysM^{Cre}IL-4R α ^{-/-flox} mice, following *S. mansoni* infection, the appearance of AAM Φ s during the Th2-type response was blocked, and CAM Φ s developed instead [2]. Taken together, these examples indicate that AAM Φ s are induced and recruited to the site of parasite invasion within days following helminth infections. Although in some cases IL-4/IL-13 produced by innate cells may be sufficient to trigger their differentiation, Th2 cells are generally required for their optimal activation, recruitment, and expansion. Finally, worm products can also stimulate AAM Φ s, although it seems likely that these molecules activate AAM Φ s optimally only in the context of a Th2-type cytokine environment. Intriguingly, recent studies suggest that chitin, a structural polysaccharide expressed by many parasites, can induce eosinophil and basophil IL-4 production and also AAM Φ polarization following *in vivo* administration [25].

L-Arginine metabolism is an important branch point in the differential activation leading to the development of AAM Φ or CAM Φ . IL-12 and IFN- γ , characteristic of Th1-type responses, trigger expression of iNOS, which generates nitric oxide (NO). In contrast, Th2-type cytokines IL-4, IL-13, and IL-21 induce arginase-1. Given the high affinity of arginase-1 for arginine,

increased arginase activity can lead to low bioavailability of arginine and reduced NO production. Arginase-1 converts L-arginine into urea and ornithine. In turn, ornithine amino transferase (OAT) catalyzes the conversion of ornithine into proline—important in collagen production—whereas ornithine decarboxylase (ODC) generates polyamines, which stimulate cellular proliferation. Both of these activities may augment fibrosis associated with granulomas developing around eggs during *S. mansoni* infection of mice [26]. Supporting evidence is observed in iNOS-deficient mice, in which pronounced arginase activity by AAMΦs is associated with increased liver fibrosis and granuloma size during *S. mansoni* infection [27]. However, other mechanisms may also contribute to fibrosis under physiological conditions, as *S. mansoni*-infected $\text{LysM}^{\text{Cre}}\text{IL-4R}\alpha^{-/\text{flox}}$ mice still develop liver fibrosis [2].

Control of inflammation

AAMΦs have multiple roles during helminth infection, one of which is regulation of the immune response. Although several studies have suggested that AAMΦs enhance Th2 cell differentiation [28,29], more recent *in vivo* findings indicate that in the context of helminth infection, AAMΦs are not essential for the development of Th2-type responses. Following *S. mansoni* infection, $\text{LysM}^{\text{Cre}}\text{IL-4R}\alpha^{-/\text{flox}}$ mice showed Th2-type cytokine responses similar to controls, although $\text{IL-4R}\alpha^{-/-}$ mice exhibited marked reductions in Th2-type cytokines [2]. In the memory Th2-type response to *H. polygyrus*, *in vivo* depletion of macrophages with chlodronate liposomes had no effect on the potent Th2-type cytokine response [3]. Furthermore, following *L. sigmodontis* infection, although AAMΦs could inhibit T cell proliferation *in vitro*, little effect on Th2-cell IL-4 and IL-5 was observed [23].

In marked contrast, increasing evidence now suggests a dominant role for helminth-elicited AAMΦs in controlling underlying Th1-type inflammatory responses that may otherwise contribute to pathogenesis. Helminth infections vary greatly in terms of the interplay between Th1-type and Th2-type inflammatory responses. At one extreme, the enteric immune response to either *H. polygyrus* or *N. brasiliensis*, once established, appears to be primarily Th2-type polarized, with little evidence of an underlying Th1-type response [30]. At the other extreme are responses to the intestinal nematode *T. muris* or the trematode *S. mansoni*, where a strong underlying Th1-type response can develop if the dominant Th2-type response is inhibited by IL-4R [31] or B7 [32,33] blockade. Recent studies suggest that IL-4R signaling in macrophages sustains the Th2-type cytokine response that develops following egg deposition during *S. mansoni* infection. While $\text{IL-4R}\alpha^{-/-}$ mice developed acute schistosomiasis associated with Th1-type inflammation, *S. mansoni*-infected $\text{LysM}^{\text{Cre}}\text{IL-4R}\alpha^{-/\text{flox}}$ mice sustained an intact Th2-type cytokine response similar to infected WT mice, although they still developed acute schistosomiasis leading to increased mortality. Apparently, the suppressive effect of AAMΦs occurs through a Th2 cytokine-independent mechanism, and further studies showed that this regulatory effect was also IL-10 independent [2].

Suppressive effects of AAMΦs on T cell proliferation can occur in murine models of filarial infections. *Brugia malayi* L3 injected into the peritoneal cavity can elicit AAMΦs with potent T cell suppressive properties [10]. Infection with *L. sigmodontis* also induces AAMΦs, which can suppress *in vitro* T cell proliferation. Further *in vitro* studies suggest that the mechanism of T cell suppression is independent of IL-10 and CTLA-4, but partially dependent on TGF- β [23]. Costimulatory molecules are important regulators of T cell activation, with B7-1 and B7-2 on APCs interacting with the T cell ligands CD28, to provide positive signals [34], or CTLA-4, to provide negative signals [35]. Two other B7 family members are programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), both of which bind PD-1 [36]. Recent studies suggest that these cell surface molecules may be important in macrophage-mediated T cell suppression. In particular, PD-L1 expressed by macrophages following *S. mansoni* infection can trigger T cell anergy *in vitro* following interactions with PD-1 [37].

Furthermore, in an experimental cysticercosis model, *T. crassiceps*-infected mice showed elevated expression of PD-L1 and PD-L2 on AAMΦs and blockade of either ligand interaction with PD-1 inhibited the IL-10-independent suppressive effect of AAMΦs on T cell proliferation *in vitro* [38]. Thus, AAMΦs appear to be more important in blocking underlying Th1-type responses than promoting Th2-type responses, including Th2 cells. The mechanisms through which AAMΦs function remain unclear but at least in a number of cases are apparently IL-10-independent. Considerably more investigation into the *in vivo* function of AAMΦs is required to determine their mechanism of immune downregulation during helminth infection.

Wound healing

AAMΦs can contribute to fibrosis and repair at the site of injury [39], which may be of considerable importance during helminth infection. These large metazoan parasites can cause extensive damage as they pass through tissue, releasing proteolytic enzymes that damage cells and tissue. In studies of the fibrotic response in a schistosomiasis model, mice polarized towards a Th2-type (IL-12/IL-10-deficient) response showed larger granulomas, greater eosinophilia, and upregulation of genes involved in tissue remodeling including: matrix metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs), and several types of collagens [40]. Also highly expressed were arginase-1 and ChAFs associated with AAMΦs. FIZZ1/RELMα has recently been implicated in wound healing: bleomycin-induced pulmonary fibrosis yielded increased expression of FIZZ1/RELMα [41]. Fibroblasts exposed to type II alveolar epithelial cells from bleomycin-treated rats or transfected with a FIZZ1/RELMα-expressing plasmid showed greater production of α-smooth muscle actin and type I collagen, indicating myofibroblast activation. Molecules with well-established roles in wound repair and tissue remodeling are also expressed by AAMΦs. IL-4 activation of human macrophages leads to upregulation of: extracellular matrix proteins fibronectin, tenascin-C, and βIG-H3[42]; degradative enzymes MMP-1 and MMP-12; and the matrix cross-linking enzyme tissue transglutaminase (tTG) [14]. The expression of these factors by AAMΦs was largely inhibited by dexamethasone, consistent with the inhibitory role of glucocorticoids in wound healing. These findings suggest that AAMΦs may play an important role in the repair of tissue damage, and additional studies will need to examine whether these mediators actually play an essential role in remediating tissue lesions caused by these parasites.

Worm expulsion and resistance

Elements of the Th2-type response can control pathologic Th1-type inflammation and also marshal effective helminth resistance; for example, the Th2-type response has a demonstrated role in the expulsion of several intestinal nematode parasites [43,44]. Clearly AAMΦs may contribute to resistance by controlling Th1-type immunity and thereby promoting a potent and polarized Th2-type response. However, it is becoming increasingly apparent that AAMΦs may also promote certain components of the Th2-type response important in worm expulsion. For example, AAMΦs recruit eosinophils to the lung and peritoneum during *N. brasiliensis* infection [45]. Two candidates for eosinophil recruitment are leukotriene B₄ [25] and Ym1, a chitinase-like peptide that lacks chitinase activity [46]. Related to Ym1 is a functional chitinase, acidic mammalian chitinase (AMCase), which shows elevated gene expression during *H. polygyrus* or *B. malayi* infection [3,10]. It is tempting to speculate that AMCase may function to damage chitin-containing parasites, including developing microfilaria. If so, this would be in addition to its recently described function in augmenting Th2-type responses by stimulating production of monocyte chemotactic protein-1 and eotaxin [47]. The potential multiple roles of Ym1 and AMCase during helminth infection make these related molecules compelling subjects for future investigations of AAMΦ function.

Investigation of the host protective Th2 memory response to the native mouse intestinal nematode parasite, *H. polygyrus*, has the particular advantage in that the responses are the product of host:parasite co-evolution. Primary inoculation results in chronic infection, but following drug-induced elimination of adult parasites from the gut, subsequent challenge inoculation results in parasite clearance within two weeks [43]. The parasitic L3 enter the small intestine and rapidly take up residence in the submucosa region, returning to the gut lumen as adults 8 days later. By day 4 after secondary inoculation, neutrophils and AAMΦs surround the parasite, forming a Th2-type granuloma, and a band of CD4⁺ T cells and CD11c⁺ dendritic cells surround the macrophages. Chlodronate liposome treatment to deplete macrophages, or administration of an arginase inhibitor, caused marked increases in larval mobility, decreases in stress-induced larval cytochrome oxidase activity, and reductions in adult worm expulsion [3]. These studies thus suggest that AAMΦs are essential in the development of the *H. polygyrus* protective immune response. Future studies need to address the arginase-dependent mechanism leading to larval damage by AAMΦs.

Conclusion

It is now clear that the first responders during Th2-type, as well as Th1-type, responses to infectious pathogens include macrophages. In both cases, although macrophages are important in the initial stages of the response, their further differentiation, expansion, and optimal effector function is dependent on T cell help. In the case of helminth infection, AAMΦs express molecules that in many cases are well-suited for the development of host protective responses against these large multicellular parasites, including recently characterized ChAFFs and products of arginine metabolism. These AAMΦ effector functions can be generally separated into three categories contributing to the host protective response: control of Th1-type inflammation, wound healing, and worm expulsion. Future studies of the role AAMΦs play in helminth infection should provide new insights into how the Th2-type response mediates resistance and control of pathologic inflammation.

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Figure 1. Macrophage differentiation in response to different pathogens

Depending on the cytokine environment, as well as the presence of specific pathogen associated structures, macrophages can differentiate into classically or alternatively activated macrophages. Helminths induce alternatively activated macrophages, which upregulate arginase and which may be important in several aspects of host protection: parasite resistance, dampening harmful associated inflammation, and wound healing necessary to repair the damage caused by these large invasive multicellular parasites. In contrast, many microbes trigger classically activated macrophages, which upregulate iNOS, resulting in nitric oxide production, and can contribute to pathologic inflammation.