

## Review Article

# Similarity and Diversity in Macrophage Activation by Nematodes, Trematodes, and Cestodes

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This review summarizes current knowledge of macrophages in helminth infections, with a focus not only on delineating the striking similarities in macrophage phenotype between diverse infections but also on highlighting the differences. Findings from many different labs illustrate that macrophages in helminth infection can act as anti-parasite effectors but can also act as powerful immune suppressors. The specific role for their alternative (Th2-mediated) activation in helminth killing or expulsion versus immune regulation remains to be determined. Meanwhile, the rapid growth in knowledge of alternatively activated macrophages will require an even more expansive view of their potential functions to include repair of host tissue and regulation of host metabolism.

## 1. Introduction

Since the discovery in the late 1980s that T helper cells exhibit distinct cytokine profiles, the unique immunological profile associated with helminth infection has been explained by the activation of the Th2 cell pathway. In particular, the dramatic increase in numbers of eosinophils, mast cells, and IgE could be directly explained by cytokines produced by the Th2 subset. More recently, we have come to appreciate that in addition to eosinophils and mast cells, “alternatively-activated” macrophages (AAM $\Phi$ ) are a characteristic feature of the polarized Th2 response. Macrophages at helminth infection sites were termed AAM $\Phi$  because they exhibited specific characteristics, such as arginase 1 production, that had been observed when macrophages were exposed *in vitro* to IL-4 [1–3]. Siamon Gordon and colleagues described this as an alternative activation pathway that contrasted with the “classical” activation by LPS and IFN $\gamma$  [4, 5]. With further exploration of the *in vivo* phenotype, it has become apparent that AAM $\Phi$  express a whole range of molecules that distinguish them from classically activated macrophages (CAM $\Phi$ ) [6–9].

What has been remarkable is the consistency of the findings between the diverse laboratories and infectious

models in which these cells have been studied, with identification of the same key molecules (arginase 1, resistin-like molecule [RELM]  $\alpha$ , Ym1, etc.) expressed during helminth infection (see table in Reyes & Terrazas review [10]). This is remarkable because “helminths” represent an enormously diverse range of pathogens with entirely different phylogenetic origins and life histories. Indeed, the AAM $\Phi$  phenotype seems to occur in any strong Th2 environment including allergy and some chronic microbial infections [10–12]. The commonality of these findings has, perhaps erroneously, suggested to us that we could define a broad function for these cells analogous to microbial killing for CAM $\Phi$ . However, despite an ever-broadening definition of AAM $\Phi$  and their associated markers and characteristics, we are still essentially ignorant of their *in vivo* function. Perhaps it is time to explore the many differences between the models used to study AAM $\Phi$  and consider that these cells may function differently depending on context.

## 2. Helminths and Th2 Immunity

*2.1. Helminth Phylogeny.* Helminth parasites are routinely used as models to study T helper cell polarization and

as a result, our understanding of Th2 subset development and control has become increasingly sophisticated [13–17]. However, it is important to appreciate that to draw broad conclusions from experiments with schistosomes and then apply these to nematode parasites (or vice versa), is potentially misleading. Despite the common terminology, the only shared biological features of many “helminthes” are their metazoan origins and the ability to infect mammals. Schistosomes are part of the platyhelminths that include the cestodes (tapeworms) and other trematodes (flukes or flatworms). The phyla Nematoda (roundworms) include hookworms, whipworms, and filarial parasites. The split that led to Platyhelminthes and Nematoda occurred over 1 billion years ago, long predating the split between vertebrates and invertebrates [18]. Nematodes are the most abundant animal on earth both in terms of total numbers and numbers of species. Within this group of animals, parasitism has independently evolved many times [19] and parasitic nematodes represent an enormous burden in terms of human, animal, and even plant health. In terms of human disease, platyhelminths infect fewer numbers but are responsible for higher levels of morbidity and mortality [20].

**2.2. Th2-Biased Immunity.** The utility of helminths as models to study Th subset bias stems from the striking feature that, despite their phylogenetic diversity, they all induce profound Th2 responses, characterized by CD4<sup>+</sup> T cells producing IL-4, IL-5, IL-9, IL-10, and IL-13 among others. However, recently it has become apparent that even the Th2 subset itself is enormously complex, with T cells that specifically function to provide B cell help and produce IL-4 but not the other signature Th2 cytokines (follicular helper cells) [15], specific IL-9 producing cells [21], and other T helper subsets that produce Th2 cytokines such as the recent discovery that IL-10 is produced by Th1 cells [22]. In an adaptive immune response, macrophages ultimately respond to T cell derived cytokines, and a sustained alternative activation phenotype absolutely requires CD4<sup>+</sup> Th2 cells [23]. Thus, differences in Th cell cytokine profiles in different tissues and in response to distinct parasites will determine differences in macrophage activation.

**2.3. Nematodes, Trematodes, and Cestodes and the Induction of the Th2 Response.** Although virtually all helminths induce Th2 cytokines, the pattern and magnitude of these responses differ widely due to not only the vast differences in the biology of the pathogens as mentioned above, but also their broadly different migration and eventual host niche. Nematodes typically drive strong type 2 cytokine responses from the onset of infection. Indeed, within hours of infection innate activation of the Th2 pathway can be detected [23–26]. However, even within the nematode phyla the intensity of this early type 2 response varies, perhaps reflecting the differential ability of nematodes to inhibit the type 1 inducing cytokine, IL-12 [27].

Eggs released by the schistosome parasites are believed to be the strongest known inducers of Th2 cytokines in mammals, and yet the invasive cercariae induces only

a moderate Th2 response that is matched by a Th1 response of similar magnitude [28]. This initial mixed response is swamped by the extraordinarily high Th2 response generated to the eggs produced when the adult pairs reach sexual maturity [29]. Because of its importance as a cause of human morbidity and the availability of excellent mouse models, far more is known about the immunology of schistosome infection than other trematodes. However, *Fasciola hepatica*, a liver fluke that predominantly infects sheep and cattle, has also been studied in mouse models. Consistent with indicators of type 2 immunity in cattle, *F. hepatica* infection of mice results in a dominant Th2 response that has the capacity to suppress Th1 responses [30].

Cestodes are also dramatically understudied despite their capacity to cause severe disease in animals and people. Nonetheless, the data is consistent with the general helminth literature in that cestodes by and large have a strong propensity to drive Th2 immune responses. Similar to responses to schistosomes, peritoneal implantation of BALB/c mice with *Taenia crassiceps* metacestodes results in an initially weak mixed Th1/Th2 response that becomes strongly Th2 dominated as infection progresses to the chronic phase [31, 32]. However, there are resistant mouse strains that expel the parasite in the acute phase due to the dominance of IFN $\gamma$  production [33]. Responses to peritoneal infection with *Echinococcus granulosus* protozoa are unusual in that the initial Th2 responses that dominate early (week 1) become more mixed, with emergence of IFN $\gamma$  production as infection progresses (week 4) [34].

**2.4. Protective Immunity against Nematodes, Trematodes, and Cestodes.** In addition to the differences in the kinetics and magnitude of Th2 induction, the role of Th2 immunity in host protection varies substantially between these different parasites. Indeed, the paradigm that Th2 immunity is acting to destroy or expel worms is by no means universal.

The scenario in which there is an absolute requirement for Th2 immunity in host protection is that of the gastrointestinal nematodes. Expulsion of all GI nematodes studied to date is exquisitely dependent on Th2 cells. However, the specific cytokines (IL-4, IL-5, IL-9, IL-10, IL-13 among others) and the effector cells on which they act (epithelial, smooth muscle, mast cell, macrophage, nerve) vary tremendously depending on the location of the parasite, as well as its invasive properties. The situation with nematodes, such as the filariae, that live entirely in the tissues is somewhat different. Although Th2 responses are required for worm killing [35], Th1 immunity and particularly IFN $\gamma$ , rather than inhibiting the anti-parasite Th2 response, act synergistically with IL-5 to kill the adult stage of the parasite [36]. In the case of these tissue-dwelling nematodes, our increased understanding of the cytokine pathways required for parasite destruction has still left us in the relative dark as to the actual killing mechanism(s).

During schistosome infection, Th2 responses are essential for host survival but this has little to do with detrimental effects on the parasite. This is largely due to the fact that pathology is the result of the egg deposition stage and

it appears that in the absence of a Th2 response (or a Th1 response for that matter), the egg is highly tissue destructive. Death can occur either due to overwhelming gut inflammation and sepsis or liver damage [37]. Additionally, Th2 responses to the egg promote fibrosis that itself can be a major cause of morbidity [38].

Cestodes provide an unusual perspective, in that despite inducing a potent Th2 response, protective immunity can require Th1 cells [33, 39]. Indeed, dominance of Th2 responses during infection with *T. crassiceps* leads to susceptibility to infection mainly through the suppression of Th1-driven nitric oxide (NO) production, a key effector molecule against these parasites [32, 39]. However, cestodes are also unusual in that there is little consistency in immunological mechanisms that protect against infections within this group. In this respect, resistance to *E. granulosus* actually increases in the absence of NO production [40], possibly due to the absence of the considerable suppressive effects on proliferation that this molecule exerts in echinococcosis [41].

### 3. The Molecular Profile of AAM $\Phi$

AAM $\Phi$  are becoming increasingly recognised as a key effector arm of the Th2 immune response, but their actual function in different helminth infections has yet to be unravelled (see below) and is likely to be as diverse as the role of Th2 immunity itself. The concept of “alternative macrophage activation” was introduced by Siamon Gordon and colleagues in the early 1990s to describe the in vitro response of macrophages to the Th2 cytokines IL-4 and IL-13 [4, 5]. Significantly, the term AAM $\Phi$  was coined to highlight the activated nature of these cells that distinguished them not only from macrophages classically activated by microbial products and Th1 cytokines (CAM $\Phi$ ), but from deactivated macrophages in which costimulatory molecules and class II expression are suppressed by down-regulatory cytokines such as IL-10. The two features that distinguished AAM $\Phi$  in vitro were the expression of arginase 1 and the mannose receptor. The requirement for IL-4 and/or IL-13 was subsequently confirmed in vivo, using gene-deficient mice [6, 11, 42, 43].

Realization that the AAM $\Phi$  described in vitro were a feature of helminth infection came from studies of *Schistosoma mansoni* and *Brugia malayi* [6, 43]. Both studies verified IL-4 dependent arginase 1 expression by macrophages in vivo, but the *B. malayi* study additionally identified novel IL-4 dependent genes associated with this phenotype including Ym1 and RELM $\alpha$ /FIZZ1 [6]. The highly unique profile was rapidly confirmed across the full range of helminth infections [7, 44–48]. Although Ym1 and RELM $\alpha$  were discovered in vivo, the direct induction of these genes by IL-4 and/or IL-13 was also demonstrated in vitro [2, 3]. It should be noted here that IL-4 and IL-13 both utilize the same signal transducing receptor chain, the IL-4 receptor  $\alpha$  (IL-4R $\alpha$ ), which explains the considerable overlap in function of these cytokines. Which of these cytokines is more important for alternative activation of macrophages in vivo remains to be fully determined, however, a recent report using mice

deficient for the IL-13 receptor  $\alpha$ 1 subunit suggests that IL-13 is dispensable for expression of Ym1 and RELM $\alpha$  but not arginase in the liver during *S. mansoni* infection [49].

A molecular signature for AAM $\Phi$  (defined here as an IL-4/IL-13 dependent phenotype) has arisen that is represented by the three most abundant IL-4/IL-13 dependent gene products: Ym1, RELM $\alpha$ , and arginase 1. *Ym1* is a member of the family 18 chitinases but has no chitinolytic activity and is thus referred to as a chitinase-like molecule [50]. Other members of this family in mice include Ym2 and acidic mammalian chitinase (AMCase), the latter functioning as a true chitinase. Ym2 and AMCase are also IL-4/IL-13 inducible proteins and the similarity between Ym1 and Ym2 is so high that most studies do not actually distinguish between them. All antibodies to date recognize both, and most PCR methods do not distinguish them, although this is possible with careful primer design. Thus, unless a study clearly identifies a specific Ym protein, it might be appropriate to use the more ambiguous designation Ym1/2. RELM  $\alpha$  was first described in a lung asthma model, where it was described as FIZZ1 [51], but was subsequently identified as a member of a family of cysteine-rich molecules related to resistin, a hormone involved in glucose metabolism [52]. *Arginase 1* is the best studied of these proteins and has well-established roles in regulating NO production by competing with iNOS for their common substrate L-arginine [1], as well as inhibition of T cell responses through L-arginine depletion [53]. The arginase pathway additionally leads to the production of proline and polyamines, which contribute to tissue repair and fibrosis [54]. Subsequently there has been identification of numerous other markers associated with the alternative activation phenotype [7, 9] and this number is likely to grow as more extensive transcriptomic and proteomic analyses are undertaken [55].

Macrophages with an AAM $\Phi$  phenotype characterized mainly by arginase 1 production also arise in protozoan (reviewed in [10]) and certain bacterial infections [56]. In cutaneous leishmaniasis (*Leishmania major*), this AAM $\Phi$  phenotype is dependent on signaling through the IL-4R $\alpha$  chain [57] as in helminth infection models [6, 11, 42]. However, a STAT6-independent pathway also leads to arginase 1 expression during *Mycobacterium tuberculosis* and *Toxoplasma gondii* infections, which in the former is dependent upon TLR signaling [56]. The main effect of arginase 1 expression in all of these settings appears to be an increase in susceptibility to infection through diversion of L-arginine from production of the reactive nitrogen intermediates that kill these pathogens [10, 56].

As interest in these cells grew, the term “alternatively-activated” came to include any cell displaying an alternate phenotype to CAM $\Phi$ . Subdivision of the M1 and M2 terminology has helped to address this issue with M1 equating with CAM $\Phi$  while M2 includes M2a, M2b, and M2c. M2a most closely reflects the IL-4/13 dependent phenotype originally associated with AAM $\Phi$ , while M2b includes activation by other modulators such as immune complexes that lead to high IL-10 production and M2c reflecting the more deactivated phenotype associated with IL-10 treatment in vitro [58]. Nonetheless, the difficulty in

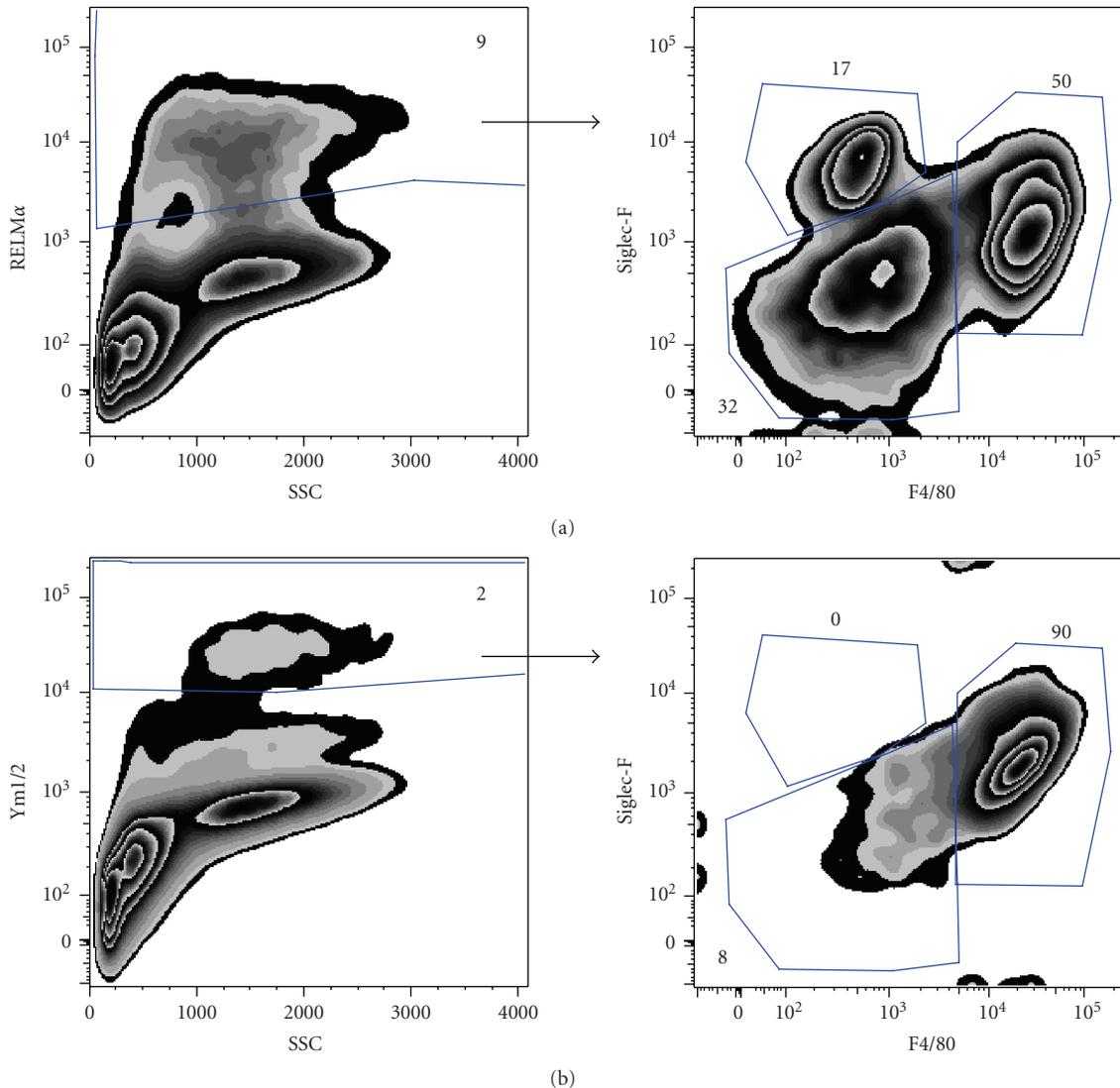


FIGURE 1: RELM $\alpha$  and Ym1/2 expression in the pleural cavity during *L. sigmondontis* infection. *Left-hand plots*: Flow cytograms depicting side scatter (SSC) versus RELM $\alpha$  (a) or Ym1/2 (b) of pleural cavity cells 12 days post infection with *L. sigmondontis*. The gates for RELM $\alpha$ <sup>+</sup> and Ym1/2<sup>+</sup> cells were set using isotype control staining. The proportion of cells positive for RELM $\alpha$  and Ym1/2 in naïve mice was 1.5% and 0.05%, respectively. *Right-hand plots*: Siglec-F versus F4/80 expression on Ym1/2<sup>+</sup> or RELM $\alpha$ <sup>+</sup> cells. Numbers in italics represent percentage of cells within the neighbouring gate.

finding appropriate terms is a reflection of the enormous diversity in macrophage phenotype found both in vivo and in vitro [59], as well as their capacity to rapidly alter their expression profile in response to a new set of environmental signals [60].

A current difficulty in delineating the functions of AAM $\Phi$  is that many of the “signature” AAM $\Phi$  molecules are not restricted to macrophages. The availability of good antibodies for intracellular staining and fluorescence microscopy, the creation of mice that report gene expression, and the ability to sort cell subsets prior to gene expression analysis have greatly increased our knowledge of the range of cells that show an “alternative-activation” phenotype, as well

as the comparative breadth of expression of the different AAM $\Phi$  markers. For example, in liver granulomas from mice infected with *S. mansoni*, the main producer of RELM $\alpha$  appears to be eosinophils rather than macrophages [61], whilst in lung granulomas induced by i.v. injection of schistosomula, RELM $\alpha$ <sup>+</sup> cells are comprised of macrophages, eosinophils, and airway epithelial cells [62]. In the serous cavities of mice infected with *Litomosoides sigmondontis* or *B. malayi*, we have observed a similarly broad pattern of RELM $\alpha$  expression, with mature macrophages (F4/80<sup>hi</sup> Siglec-F<sup>-</sup>), eosinophils (Siglec-F<sup>hi</sup> F4/80<sup>lo</sup>), and F4/80<sup>lo-intermediate</sup> Siglec-F<sup>-</sup> cells that include DC, all capable of making this protein (Figure 1(a) and data not shown). Expression of Ym1/2 is

markedly different, being almost exclusively restricted to F4/80<sup>hi</sup> Siglec-F<sup>-</sup> mature macrophages (90%), and with no expression detectable in eosinophils (Figure 1(b)). However, Ym1/2, like RELM $\alpha$  can also be expressed by epithelial cells in the lung [61, 63, 64] and both Ym1/2 and RELM $\alpha$  appear to be a feature of many types of antigen presenting cell found in the lymph nodes draining helminth infection sites [46]. Thus, it is now apparent that many cell types can show an “alternative-activation” phenotype, with chitinase- and resistin-family members prominent. Epithelial cells in particular express not only Ym1/2 and RELM $\alpha$  during Th2 immune responses but related family members including the true chitinase, AMCase [63] and RELM $\beta$  [65]. Of the three most abundant AAM $\Phi$  markers [6], arginase 1 appears to have a more macrophage-restricted expression profile. This was demonstrated by Reese et al. using mice that contain an IRES-YFP knock-in allele that reports arginase 1 expression, in which extra-hepatic arginase 1 expression was macrophage-restricted in the lung or peritoneum of *Nippostrongylus brasiliensis* infected or chitin injected mice, respectively [66].

Another major difficulty has been efforts to translate our understanding of murine AAM $\Phi$  to humans, not only because some of the mouse defined AAM $\Phi$  markers are not present in the human genome, but because the relevant tissues cannot be readily accessed. An example of this problem has been the argument over whether human macrophages express arginase 1, strongly reminiscent of earlier arguments about NO production [67]. It may be that arginase 1 expression is more limited in human macrophages or that we have just not yet identified the right tissues. Indeed, arginase 1 can be induced in human macrophages by IL-4 [68] and can be observed in monocytes of filarial-infected individuals [69].

Even more problematic has been the realization that Ym1 is not even present in the human genome. However, distribution of the family 18 chitinases (including AMCase and Ym1/2) between different mammalian species is a fascinating puzzle in itself. Mammals have two genes encoding active chitinases that represent an ancient gene duplication event and show high sequence homology to chitinases of lower organisms. The mammalian chitinase-like proteins (CLPs) that include Ym1, appear to represent more recent gene duplication events with subsequent loss-of-function mutations [70]. Thus all mammals express the highly conserved active enzymes, chitotriosidase and acidic mammalian chitinase (AMCase) but additionally express a broad range of diverse CLPs, with each mammalian species exhibiting a different complement of CLPs [70]. In mice these include Ym1, Ym2, and YKL-40/BRP-39, which have all been strongly implicated in Th2 conditions [50, 71]. Humans express YKL-40 but also a distinct CLP, YKL-39 [70]. Because no two mammals express the same set of these proteins and CLPs appear to be undergoing remarkably active evolution, no animal model can fully represent the human genes. Studying mice should nonetheless be informative as one can presume that despite species differences a common theme lies behind the evolutionary forces driving the divergence of CLPs.

#### 4. Functional Roles of AAM $\Phi$

As the molecular definition of AAM $\Phi$  becomes more refined, our hope has been that an understanding of function would follow. However, the functions of gene products associated with alternative activation, such as RELM $\alpha$  and Ym1 remain elusive and our full understanding of the contribution of macrophages during helminth infection is an increasingly active area of investigation. Considering the diversity of helminth infection and the complexity of the associated Th2 response, a single well-defined role for AAM $\Phi$  is unlikely to emerge.

*4.1. Do M $\Phi$  Promote Helminth Killing or Expulsion?* The depletion of macrophages using clodronate-loaded liposomes has provided a powerful tool by which to analyse the function of these cells during helminth infection. This technique has provided evidence that macrophages play a central role in nematode expulsion during intestinal infection, both in the memory response to a secondary infection with *Heligmosomoides polygyrus* [72], and in expulsion of primary *N. brasiliensis* infection [73]. In both these settings, parasite clearance is dependent upon a strong Th2 response, which acts to rapidly recruit immune cells including macrophages to the infection site and to stimulate their expression of Arginase 1, RELM $\alpha$ , and Ym1/2 in a STAT-6 dependent manner. Critically, blocking recruitment of macrophages via depletion of monocytes resulted in prevention of worm expulsion, whilst the Th2 response and recruitment of other inflammatory cell populations were left intact. Our understanding of macrophage function in filarial nematode attrition is more limited. However, observations that worm survival during murine peritoneal infection with either *Brugia pahangi* or *malayi* L3 larvae is enhanced following injection of carbon particles or carrageenan [74, 75] imply an effector function for peritoneal macrophages. Consistent with a role in filarial killing, macrophages make up significant proportion of the granulomas that encase dying *B. malayi* and *L. sigmodontis* worms but the conundrum is: do granulomas cause worm damage or form because the worms are already damaged?

While there is evidence for macrophage effector function during nematode infections, it is still unknown whether this occurs via direct or indirect mechanisms. Macrophages greatly increase the hypercontractility of intestinal smooth muscle during *N. brasiliensis* infection, providing a potentially indirect effector mechanism [73]. Because filarial nematodes are restricted to tissue sites during infection, it is likely a distinct though overlapping array of effector mechanisms is required to act against these nematodes. Perhaps a more likely role for macrophages in these infections is to recruit other Th2 effector cells important in nematode attrition. In this respect, eosinophils have a well-documented role in vivo, acting against larval stages of both *B. malayi* and *L. sigmodontis* [76, 77], and recent data demonstrates that recruitment of eosinophils to the peritoneal cavity following *N. brasiliensis* infection or injection of chitin is dependent on macrophages [66, 78]. An attractive possibility for a direct anti-nematode effector function is the association of AAM $\Phi$

with chitinases and chitinase-like molecules [50], which in principle have the capacity to act on chitin-containing stages of the parasite. However, as of yet, there is no direct evidence to support this.

**4.2. Is Alternative Activation Required for Anti-Worm Effector Function?** Whilst macrophages can perform as anti-nematode effector cells, the question remains whether they need to alternatively activate to exert this function. Anthony et al. [72], showed that, like macrophage depletion, an inhibitor of arginase, S-(2-boronethyl)-l-cysteine, could impair worm expulsion during secondary *H. polygyrus* infection [72]. Using the same technique, arginase I expression was also implicated as mediating expulsion of *N. brasiliensis*, although experiments were inconclusive since treatment only prevented worm expulsion in 60% of the mice despite parasite egg production and host smooth muscle hyper contractility being greatly impaired [73]. The broad-acting nature of this treatment (it blocks both arginase I and II and could potentially act directly on worms in addition to other non macrophage host cell sources) makes it hard to draw firm conclusions. A stronger case against alternative activation driving these macrophage effector mechanisms, is provided by two earlier studies both of which used mice on the same resistant BALB/c background as Zhao et al. [73]. These demonstrated that IL-4R $\alpha$  need not be expressed on macrophages/neutrophils or indeed any hematopoietic population in order for efficient expulsion of *N. brasiliensis* [79, 80]. Using the same macrophage/neutrophil-specific IL-4R $\alpha$ -deficient mice, it has also been shown that alternative activation of macrophages is not required for expulsion of another intestinal nematode *Trichinella spiralis* [81]. Other potential effector functions of “Th2-associated” macrophages may also be independent of alternative activation state, as for example, macrophage-dependent-recruitment of eosinophils in response to chitin injection is STAT6-independent [66]. It is quite conceivable that in Th2 infections, macrophage effector function could be completely independent of AAM $\Phi$ -associated molecules or that expression of arginase 1 or other AAM $\Phi$ -associated molecules could be induced by an IL-4R $\alpha$ -independent mechanism, for example via a TLR-dependent event [10, 56] such as exposure to gut flora. Unfortunately, the expression of either arginase 1 or other AAM $\Phi$  associated markers was not investigated in the intestinal tissues of *N. brasiliensis* or *T. spiralis* infected M $\Phi$ /neutrophil-specific IL-4R $\alpha$ -deficient mice [79, 81]. Comparative analysis of the susceptibility of mice which lack, in macrophages specifically, either IL-4R $\alpha$  or “alternative activation” proteins such as arginase 1 would help considerably to resolve the issue of the function of alternative activation “per se” in intestinal nematode infections. Interestingly, a study with such mice has shown that arginase 1 expression by AAM $\Phi$  has no host protective effect against primary infection with the trematode *S. mansoni* [82].

**4.3. Can CAM $\Phi$  Act against Helminths?** In contrast to the ambiguity surrounding alternative activation in immunity to

nematodes, it is clear that the reactive oxygen or nitrogen species can damage most types of helminth parasites [39, 83–86]. However, only in cestode infection do reactive nitrogen species and CAM $\Phi$  appear to function against the parasite in vivo. In murine cysticercosis (*T. crassiceps*) blocking of iNOS using the inhibitor L-NG-monomethyl arginine leads to increased parasite burdens [39]. Consistent with this, induction of Th2 responses and STAT-6 signaling underlie susceptibility to infection, whilst Th1 responses and STAT-4 signaling underlie resistance [32, 33]. However, as mentioned above, this is not a requirement in immunity to all cestodes. Indeed, NOS2 deficient mice, which are incapable of making iNOS, are actually less susceptible to infection with the cestode parasite *E. multilocularis* [40]. In this infection CAM $\Phi$  appear to have a pathological effect, most likely due to the direct immunosuppressive effect of NO on cell proliferation [87].

Given the divergence of the helminth parasite phyla and the host tissue sites they have chosen to infect, it is perhaps unsurprising that diverse effector mechanisms are required for immunity to different infections [44, 88]. However, a common thread is that macrophages can act against both nematode and platyhelminth infections, and there is still no published evidence of any infection in which macrophages can be dispensed at no cost to resistance. The mechanisms employed by the macrophages though are seemingly disparate. As discussed below, AAM $\Phi$  do play an important role in protecting the host in schistosomiasis by limiting parasite-mediated tissue damage rather than mediating killing [79]. Indeed as we struggle to identify direct antihelminth effects of AAM $\Phi$ , the evidence builds that the macrophage products most associated with alternative activation such as arginase 1 and RELM $\alpha$  have profound inhibitory effects on host immunity, including the Th2 response itself [61, 62, 82]. This raises the possibility that the alternative activation state of macrophages does not function primarily as an effector arm but has critical regulatory or parasite disposal (rather than killing) roles.

**4.4. AAM $\Phi$  Are Potent Suppressors of Cellular Proliferation.** One property of activated macrophages that is consistently observed in a wide variety of systems is the ability to block the proliferation of cells with which they are cocultured. This feature has been well described for CAM $\Phi$  in which the antiproliferative properties of NO are responsible [87]. Myeloid cells derived from helminth infected animals also exhibit similar antiproliferative properties [60, 89–91]. Importantly, it can be replicated in vitro by treatment of macrophages with IL-4 or IL-13 [2, 60] and in vivo is reliant on IL-4 and/or IL-13 in certain settings [89]. Indeed, the ability to inhibit cellular proliferation is a defining characteristic of AAM $\Phi$ . Despite the near-universal finding that AAM $\Phi$  suppress cellular proliferation ex vivo, the in vivo significance is not known. Understanding the relevance of this proliferative suppression has been complicated by the fact that, unlike CAM $\Phi$ , a single mechanism for proliferative inhibition has not been identified. Instead a multitude of pathways have been found that differ depending on the infection context (reviewed in [44]) and include Programmed

death ligand (PD-L) interactions [92, 93], TGF- $\beta$  production [94], lipid mediator release [95], IL-10 production [96, 97], and L-arginine depletion [82]. There appear to be three categories of proliferative suppression generally observed during helminth infection: contact and IL-4 dependent, contact dependent and IL-4 independent, and finally IL-4 dependent and contact-independent. No doubt the target cells will also differ depending on the pathways involved, with some mechanisms, such as the PD-L pathway seen during infection with the platyhelminths, *T. crassiceps*, and *S. mansoni* [92, 93], affecting predominantly T cells. Other mechanisms have a broader target including even tumor cells that typically have no restriction on cell division [89].

One cannot overemphasize the diversity of suppressive mechanisms observed. For almost every mediator identified as critical for AAM $\Phi$ -mediated suppression of T cells, there is another study that finds that mechanism dispensable. This disparity could be due to the distinct biological mediators released by these vastly different parasites, which presumably all favour an immuno-suppressive environment. However, many other factors could account for this diversity, from differences in the magnitude and bias of the Th cell response to tissue localization. Of interest, proliferative suppression is also a feature of myeloid-derived suppressor cells (MDSC), which share many features with AAM $\Phi$  but are associated with cancer and other immune suppressive environments rather than helminth infection [98]. T cell suppression by MDSC is mediated by both iNOS-driven production of NO and arginase 1-driven depletion of L-arginine [53]. L-arginine is essential for T cell activation [99] but L-arginine depletion could also lead to production of suppressive reactive oxygen intermediates [95, 100]. This is similar to recent data showing that macrophage-derived arginase 1 is required to suppress the proliferation of T cells from *S. mansoni*-infected mice [82] but also during non-healing *Leishmania major* infection, which is associated with AAM $\Phi$  [1]. Although arginase 1 is emerging as one of the most important mediators of proliferative suppression, it is not the full story. Chemical blockade of arginase 1 had only a small impact on suppression mediated by AAM $\Phi$  from the peritoneal cavity of *B. malayi* implanted mice, and full IL-4-dependent suppressive capacity was maintained when arginase expression was reduced by LPS/IFN $\gamma$  treatment [60].

Finally, it is important to consider that NO mediated suppression, although most strongly associated with microbial infection, also has a role to play during helminth infection. As already mentioned, NO can act as an effector molecule during infection with the cestode *T. crassiceps* [39]. However, within the same infection model [95], and infection with *E. multilocularis* [41], NO mediated suppression by peritoneal cells has been observed. Even in filariasis, where the IL-4 dependent AAM $\Phi$  suppressive phenotype has been well described, NO-mediated suppression can play a role [101].

**4.5. AAM $\Phi$  as Antigen Presenting Cells.** In line with the immuno-suppressive effects of AAM $\Phi$  described above, one

of the most consistent findings in human studies is that individuals infected with helminth parasites exhibit profound defects in lymphocyte proliferation [102–105]. One popular hypothesis has been that monocytes or macrophages from infected individuals were somehow defective in their antigen presentation capacity. However, as the discovery of alternative activation emerged and their capacity to actively block cellular proliferation was revealed the expectation shifted somewhat. Further, by definition AAM $\Phi$  are activated and thus might be expected to express good levels of class II and costimulatory molecules. Not surprisingly, the analysis of macrophage APC activation state during helminthiasis has been shown to vary considerably with infection. However, expression of antigen presentation-associated molecules is frequently intact or elevated, consistent with an “activation” profile. Mice carrying schistosome infections show marked up-regulation of MHCII but not CD80 or CD86 by splenic macrophages [93]. Transient up-regulation of co-stimulatory molecule and MHCII expression on lung macrophages occurs during the period *N. brasiliensis* larvae migrate through the lung but is quickly lost thereafter [106]. Following peritoneal implant of adult *B. malayi*, macrophages exhibit relatively high levels of MHCII, CD80, and CD86 expression compared to thioglycollate elicited M $\Phi$ , but not compared to LPS-stimulated cells [60]. Perhaps the strongest activation is seen in *T. crassiceps* infected mice, where MHCII, CD40, and CD86 but not CD80 are greatly up-regulated over an 8-week period [91]. However, this is by no means a feature of cestode infection, since the one documented parasitic helminth that leads to a reduction in activation state compared to naïve M $\Phi$  is *E. multilocularis* although only expression of CD40 is reduced whilst CD80 and CD86 remained unchanged [107].

A number of labs have investigated M $\Phi$  expression of B7 family members PD-L1 and PD-L2, with a diversity of findings in nematode, trematode, and cestode models. Independent of parasite species, Loke et al. defined PD-L2 as a marker for AAM $\Phi$ , specifically up-regulated by IL-4 in a IL-4R $\alpha$ /STAT-6 dependent manner and PD-L1 as a Th1-associated ligand [108]. However, neither PD-L1 or PD-L2 are up-regulated on peritoneal AAM $\Phi$  elicited by the nematode *B. malayi* [60]. In contrast, both ligands are up-regulated in the lung following but not during *N. brasiliensis* larval migration [106]. Similar dichotomy exists in the response to platyhelminths, with only PD-L1 up-regulation in response to *S. mansoni* infection [93], yet PD-L1 and PD-L2 up-regulation in response to *T. crassiceps* [92]. Significantly in these two settings, PD-L1 and/or PD-L2 act to potentially block the proliferation of T cells and are thus at least in part responsible for the contact-dependent proliferative suppressive effect of AAM $\Phi$  discussed above.

How then do AAM $\Phi$  perform as APC? Given that AAM $\Phi$  exhibit a profound ability to suppress cell division and fail to induce naïve T-cell proliferation, it was a surprise when initial experiments showed that AAM $\Phi$  from *B. malayi* infected mice were strong inducers of Th2 cytokine production when cocultured with naïve T-cells [109]. This ability is also shared with AAM $\Phi$  from chronic late-stage *T. crassiceps* infection [91]. Interestingly, the capacity to

drive Th2 cytokine production correlated with alternative activation, as adherent peritoneal cells from early-stage infection induce more of a mixed Th1/Th2 response while showing much lower expression of RELM $\alpha$  and Ym1/2 [91]. It remains to be determined whether the ability to drive Th2 cytokine production is a shared function of AAM $\Phi$  from all helminth infections. The difficulty in extracting AAM $\Phi$  in sufficient quantity from tissues, such as the gut lamina propria, has so far prohibited analysis of APC function in many settings, particularly intestinal infections.

It is tempting to draw a parallel to dendritic cells (DC) obtained from schistosome infected mice or exposed to helminth products *in vitro*. These exhibit a muted activation phenotype, with little change in expression of costimulatory molecules, and limited up-regulation of MHCII. However, they also efficiently promote Th2 polarisation and cytokine production [110–112]. Furthermore, DC can exhibit an alternative activation phenotype *in vitro* [46, 113] and during infection [46] or allergy [114], up-regulating expression of Ym1/2 and RELM $\alpha$  in an IL-4/IL-13 dependent manner [46, 113, 114]. Indeed, experiments looking at the ability of “alternatively activated” DC to drive Th2 responses *in vitro* and *in vivo* have identified Ym1/2 as a key molecule involved in the process [113, 114]. Ym1/2 appears to exert this effect by binding to 12/15-lipoxygenase and blocking production of PPAR $\gamma$  ligands [114], which are thought to have immunoregulatory effects on macrophages and T cells [115]. Given the large quantities of Ym1/2 produced by AAM $\Phi$  it is quite possible they also influence Th2 priming via this molecule.

#### 4.6. AAM $\Phi$ as Negative Regulators of Th2 Immunity

**4.6.1. RELM $\alpha$ .** The discovery that two novel proteins (Ym1 and RELM $\alpha$ ) were secreted in abundance by macrophages activated during helminth infection [6] led rapidly to the speculation that these would be effector molecules against the metazoan invaders. This was supported by the realisation that Ym1 was a member of a family of chitinases with presumed defensive roles against chitin-containing pathogens such as nematodes. More direct (but still circumstantial) evidence came with the recognition that RELM $\beta$ , another resistin family member, was abundantly secreted by epithelial cells in the intestines of nematode infected mice and bound directly to the chemosensory structures of the parasite [65]. The expectation naturally followed that similar anti-parasite roles would be identified for macrophage-derived RELM $\alpha$ . However, two recent papers utilizing RELM $\alpha$ -deficient mice have turned that idea on its head and instead identified RELM $\alpha$  as a critical regulator of Th2 immunity [61, 62]. Using models of *S. mansoni* and *N. brasiliensis* infection, and schistosome egg-induced lung granuloma formation, RELM $\alpha$  was shown to limit Th2-mediated immune pathologies by suppressing Th2 but not Th1 cytokine production. Importantly, this was mediated at least in part by a direct suppressive effect of RELM $\alpha$  on cytokine production by Th2 cells, as RELM $\alpha$  bound to Th2 cells and could exert this suppressive effect on T cells cultured

alone *in vitro* [62]. RELM $\alpha$  could also be detected bound to other cells, including macrophages and DC (but not Th1 cells) suggesting other non T cell mediated functions for this molecule. It is worth noting that macrophages appeared to be only a minor source of RELM $\alpha$  in the lung and liver in these studies, perhaps explaining why Th2 responses remain normal during *S. mansoni* and *N. brasiliensis* infections in macrophage/neutrophil-specific IL-4R $\alpha$  deficient mice [79].

**4.6.2. Arginase 1.** Given that one of the downstream products of arginase-mediated L-arginine catabolism is a major component of collagen, it has been widely assumed that AAM $\Phi$  would promote the fibrotic pathologies associated with chronic Th2 stimuli. However, a recent elegant study using mice in which macrophages were deficient in arginase 1 expression has demonstrated that in fact, arginase 1 negatively regulates Th2 responses and actually suppresses Th2-mediated fibrosis [82]. In contrast to the effects of RELM $\alpha$  documented by Nair et al. [62], arginase 1 expression by macrophages impaired IFN- $\gamma$  production by T cells in addition to down regulating output of Th2 cytokines. T cell proliferation in the draining lymph node was also exaggerated in the absence of arginase 1 expression by macrophages [82]. Importantly, this data confirms an *in vivo* role for arginase 1 in proliferative suppression mediated by macrophages, but extends this to show that macrophages also exert an inhibitory effect on cytokine production. Critically, they demonstrate that macrophages exhibit an overall inhibitory effect on fibrosis during schistosomiasis via their production of arginase 1.

**4.7. Summary of AAM $\Phi$  as Regulators of Th2 Immunity.** One caveat to the conclusion that AAM $\Phi$  have a critical function in the regulation of Th2 cytokines in both nematode and platyhelminth infections is the fact that Th2 generation in both the secondary lymphoid organs and the infection site (in which AAM $\Phi$  are present in greatest numbers) appeared unaffected by either the absence of IL-4R $\alpha$  signaling in macrophages or the depletion of macrophages, during *S. mansoni*, *N. brasiliensis*, and *T. spiralis* infection, and *H. polygyrus* and *N. brasiliensis* infection, respectively, [72, 73, 79, 81]. It cannot be ignored that because the role of macrophages in Th2 generation was not the main focus of these studies, the methodology for assessing the quality and quantity of the responses was not as thorough as that described for the studies on the function of RELM $\alpha$  [61, 62], arginase 1 [82], and Ym1/2 [113, 114]. It is possible though, that the removal of macrophages, or their alternative activation state, takes away both negative (RELM $\alpha$  and arginase 1) and positive (Ym1/2) regulatory signals such that the net effect on Th2 responses is nil. Whilst an *in vivo* role for arginase 1 production specifically by macrophages in Th2 regulation during schistosome infection cannot be denied, we await confirmation that RELM $\alpha$  and Ym1/2 production by these cells plays a major role in regulation of Th2 cytokine production *in vivo*. It may well be that “alternatively activated” DC and cells such as basophils play the greater role in Th2 response induction, maintenance, and

regulation. With the recent recognition that basophils are a critical APC in promoting Th2 cell activation [14, 116], it would be of interest to know whether Ym1/2 is produced by these cells.

**4.8. AAM $\Phi$  as Cells That Repair Damage to the Host.** Much of the data described above suggests that AAM $\Phi$  act as anti-inflammatory down-regulatory cells, consistent with previously proposed functions for macrophages during helminth infection [117, 118]. Additionally AAM $\Phi$  are important sources of TGF- $\beta$  and IL-10 [60, 109, 119], as well PGE2 [91] and the IL-1 receptor antagonist [119, 120]. The chemokine expression profile is also strongly associated with a non-inflammatory role [58] and with specific down-regulation of key proinflammatory cytokines by IL-4 [6, 120]. It may seem counter-intuitive that an activated cell population manifests such profoundly suppressive features. However, this could be in part explained if one sees tissue repair or wound healing as a fundamental function associated with AAM $\Phi$ . Effective tissue repair can only proceed if inflammation has been stopped [119, 121] and thus all these anti-inflammatory features may contribute to their role in repair. Early reviews on AAM $\Phi$  ascribed them a wound healing phenotype based on the production of arginase 1 [1] and angiogenic factors [1] as well as extracellular matrix components and fibronectin [122]. However, the specific role of IL-4/IL-13 in this healing phenotype versus glucocorticoids or IL-10, which the authors also considered alternative activators, was not immediately apparent. Furthermore, the relevance to helminth infection was not obvious.

Two recent papers have provided evidence that there is indeed very strong relevance to helminth infection. While investigating the kinetics of alternative activation in a model whereby *B. malayi* parasites are surgically implanted into the peritoneal cavity of mice, we noted that control animals who underwent only sham surgery exhibited transient up-regulation of Ym1/2, RELM $\alpha$ , and arginase 1 in a strictly IL-4R $\alpha$  manner [23]. However, only when both the nematode and Th2 cells were present was this alternative activation response sustained. This suggested that the induction of the signature molecules of AAM $\Phi$  was in fact an innate response to direct injury. One feature all these helminths have in common is the capacity to injure tissue in the course of their migration through the host, providing a possible evolutionary explanation for the association of Th2 immunity and wound healing [123]. The strongest evidence to date from helminth models that AAM $\Phi$  have a combined anti-inflammatory/wound healing function is in a study of *S. mansoni* infection in mice that lack the IL-4R $\alpha$  specifically on macrophages and neutrophils and thus completely lack AAM $\Phi$  but have otherwise intact Th2 responses [79]. Following *S. mansoni* infection, these mice died from overwhelming inflammatory responses in the intestine and leakage of bacteria into the blood. Although not conclusive evidence, the data strongly suggests that in the absence of AAM $\Phi$ , these mice were unable to repair the damage caused by egg migration through the intestinal wall. Further supporting a direct role for AAM $\Phi$  in wound healing, RELM $\alpha$  has angiogenic properties [124] and Ym1/2

has the ability to bind extracellular matrix [125]. The specific roles these proteins play in the complex orchestra for tissue repair and remodeling are still to be established.

## 5. Summary

Mast cells, basophils and eosinophils have long been considered the serious cellular players in the host response to helminth infection. Previously ignored, the macrophage is now taking center stage in this cellular family as one of the most important targets of Th2 immunity. This is fully appropriate when we consider that macrophages are frequently the most abundant cell type recruited to the site of helminth infection. However, it is only since the discovery of AAM $\Phi$  in vivo less than 10 years ago that a focus on these cells in helminth infection has begun. As a result, we have a long ways to go before we attain the extensive knowledge associated with CAM $\Phi$ . The challenge is to define key roles for AAM $\Phi$  while accepting that these may differ radically depending on infection stage, site, and parasite species. Macrophages are the workhorse of the immune system, and as such, can radically alter their phenotype to adapt to environmental signals [55, 59, 60]. In turn, they can actively regulate the inflammatory environment to which they are recruited or the tissues in which they reside. Using the tools available to modern scientists we can now begin to define the environmental codes that alter the AAM $\Phi$  expression profile, understand the function of the products they produce, and decipher their communication with other cells. Recent discoveries that AAM $\Phi$  are central to the regulation of host metabolism [126] mean this cross-talk is not only between cells of the immune system but with the entire organism. Unravelling this amazing complexity will keep helminth immunologists busy for years to come.

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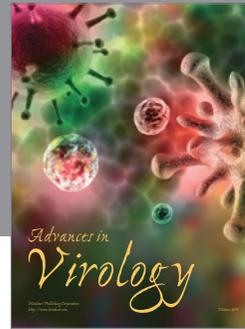
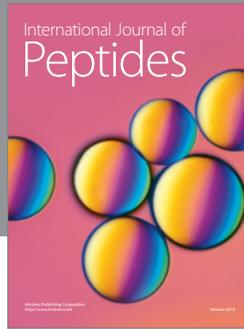
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