Review Article

Arginase in Parasitic Infections: Macrophage Activation, Immunosuppression, and Intracellular Signals

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A type 1 cytokine-dependent proinflammatory response inducing classically activated macrophages (CaM\(\Phi\)s) is crucial for parasite control during protozoan infections but can also contribute to the development of immunopathological disease symptoms. Type 2 cytokines such as IL-4 and IL-13 antagonize CaM\(\Phi\)s inducing alternatively activated macrophages (AaM\(\Phi\)s) that upregulate arginase-1 expression. During several infections, induction of arginase-1-macrophages was showed to have a detrimental role by limiting CaM\(\Phi\)-dependent parasite clearance and promoting parasite proliferation. Additionally, the role of arginase-1 in T cell suppression has been explored recently. Arginase-1 can also be induced by IL-10 and transforming growth factor-\(\beta\) (TGF-\(\beta\)) or even directly by parasites or parasite components. Therefore, generation of alternative activation states of macrophages could limit collateral tissue damage because of excessive type 1 inflammation. However, they affect disease outcome by promoting parasite survival and proliferation. Thus, modulation of macrophage activation may be instrumental in allowing parasite persistence and long-term host survival.

1. Macrophage Diversity

Macrophages are innate immune cells that play an indispensable role in the primary response to pathogens but also they play a role in the resolution of inflammation and tissue homeostasis. They can be polarized by the microenvironment to mount specific functions, as a consequence they represent a group of heterogeneous immune cells. The first indication of macrophage heterogeneity was showed by Gordon and colleagues during their studies of mannose receptor (MR) regulation in IL-4-treated M\(\Phi\) [1]. They demonstrated that macrophage treatment with IL-4 induced an alternative activation phenotype different to the classical macrophage activation (CaM\(\Phi\)), known to be dependent on interferon-\(\gamma\) (IFN-\(\gamma\)) and tumor-necrosis factor (TNF) [2–4]. Gordon later included the effects of IL-13 in the definition of alternative activation because IL-13 shares a common receptor chain with IL-4 and exerts similar effects on macrophages [5]. However, the name “alternative activated macrophages, (AaM\(\Phi\))” may have led to some confusion because it implicates that it is the only other way that macrophages can be activated. In fact, Mosser and colleagues showed later that this was the case. They demonstrated that macrophage treatment with classic stimulus, like LPS or IFN-\(\gamma\), in the presence of immune complexes induces the generation of a cellular type different from the CaM\(\Phi\). These cells release large amounts of IL-10 inhibiting the IL-12 synthesis. These M\(\Phi\) have been denominated “Type 2 M\(\Phi\)” (T2a M\(\Phi\)) because they favor the development of type II adaptive immune response [6, 7].

In 1999 Goerdt and Orfános proposed a classification of activation phenotypes based on grouping all activators other than IFN-\(\gamma\) and LPS/microbes into a common alternative activation group [8]. However, nowadays the classification has been extended. It has been proposed that a categorization in which M1 polarization included classical activated macrophages, while M2 polarization, mainly associated with antiparasitic and tissue repair programs, was subdivided in M2a or alternatively activated macrophages: M2b, corresponding to type II activated macrophages and M2c, which
includes heterogeneous macrophage deactivation stimuli such as glucocorticoids and TGF-β [9–11]. All of these types of macrophages can be found in a variety of immunological conditions, such as immune responses to different pathogens, tumors, and autoimmune diseases. Therefore, Mosser and colleagues propose a macrophage classification based on the fundamental macrophage functions such as host defense, wound healing, and immune regulation [12]. However, it is difficult to say which way is the best for classifying them. First, there are no specific biochemical markers to assign to each population. Second, it has been demonstrated that macrophages “sequentially” change their functional phenotype in response to microenvironmental changes. Therefore, macrophages can exhibit, at the same time, different kinds of markers associated with other types of macrophages [13, 14]. The plasticity of macrophages and high complexity of the in vivo environments result in the induction of various types of macrophages during protozoan infections and differentially affect the course of disease. Therefore, as a matter of simplicity, we will use the terms CaMΦ and AaMΦ. In this review we will focus on the relevance of arginase-1, an enzyme expressed in AaMΦ, in parasitic infection and how the arginase-1 expressing macrophages can be exploited by parasites. In addition, we will discuss the T cell suppressive activity of these cells and some of the complex intracellular mechanisms involved in the induction of this enzyme.

2. Arginase-1 versus iNOS

CaMΦs have on enhanced ability to present antigens and eliminate intracellular pathogens. The antimicrobial actions have been attributed to the nitric oxide (NO) release and also to the synthesis of several products of NO reaction, such as peroxynitrite [15]. NO is produced from L-arginine by the inducible isofrom of Nitric Oxide Synthase (iNOS) enzyme [16]. iNOS is induced in macrophages through the inflammatory cytokines such as TNF-α, IFN-γ, and IL-12 [17].

During infections with protozoan parasites such as *Leishmania, Plasmodium*, or *Trypanosoma*, an IFN-γ-dependent proinflammatory response triggering the development of CaMΦs is required to control parasitemia, especially during the acute phase of infection [18–21]. Therefore, CaMΦs are essential components of host defense, but their activation must be securely controlled because the cytokines and mediators that they produce can lead to host-tissue damage. On the other hand, depending on parasite virulence, host genotype and stage of infection, hosts can also produce type 2 anti-inflammatory immune responses which affect disease outcome [22, 23].

Type 2 cytokines such as IL-4 and IL-13 antagonize CaMΦs inducing arginase-1 expression in macrophages [24], a prototypic alternative activation marker in mouse macrophages [10]. The expression of arginase-1 induces a shift of arginine metabolism from NO production via iNOS toward production of L-ornithine, a precursor for polyamines and collagen, thereby contributing to the production of the extracellular matrix important for wound healing [8, 25]. Although the term “alternatively activated” macrophages has been indicated for IL-4 and IL-13, stimulated macrophages [10] factors such as IL-10 or TGF-β [5] and phagocytosis of apoptotic cells [26] also antagonize CaMΦs and induce alternative, non-M1 activation states in macrophages.

AaMΦs in normal conditions, have been identified in tissues in which it is necessary to avoid the inflammation, such as lung and placenta [8, 27]. In addition, it was demonstrated an increase in arginase activity in peripheral blood of pregnant women and in term placenta [28]. Moreover, these macrophages have been identified during the phase of remission of acute and chronic inflammatory reactions like in psoriasis and rheumatoid arthritis [29, 30]. Therefore, generation of AaMΦs after inflammation would favor the maintenance of homeostasis. Nevertheless, several evidence obtained during different infections indicate that IL-4/IL-13-dependent AaMΦs exacerbate disease by limiting CaMΦs-dependent parasite clearance and promoting parasite proliferation [31, 32]. Therefore, the successful elimination of an infectious agent depends on the existence of temporary and space signals that regulate the type of macrophage activation.

3. Arginase-1 Expressing Macrophages in Helminth Infections

Helminths are worm parasites that represent a common infectious agent in developing countries. Protection against helminths depends on IL-4 and IL-13. However, when the infection progress to a chronic stage, Th2 cytokine results in AaMΦs recruitment, which leads to fibrosis and T cell suppression [33–36]. During *Brugia malayi* experimental infection, it has been observed that the IL-4-dependent macrophage recruitment actively suppress the proliferation of lymphocytes [37]. In addition, in a model of cysticercosis, *Taenia crassiceps* infected mice showed a Th1 response in early stages of the infection, which is replaced by a Th2 in the chronic stage [35]. In contrast to other helminths infections, CaMΦs are important for the clearance of *T. crassiceps* [35]. However, in chronic stages, the Th2 response results in AaMΦs, that exhibit arginase activity [33]. It have been reported that carbohydrates present in *T. crassiceps* can produce the detrimental change from Th1 response towards Th2 during this infection [38]. Besides, it was demonstrated that previous infection of mice with the *T. crassiceps* favors parasitemia and induces larger cutaneous lesions during both *Leishmania major* and *Leishmania mexicana* coinfections. These authors postulated that helminth infection may facilitate *Leishmania* installation by inducing arginase-1 expressing macrophages [39].

On the other hand, *Schistosoma mansoni* infection, as well as the other helminth infection mentioned above, leads to the development of a Th2 cell response. Using IL-4 and IL-13 knockout mice, Brunet and colleagues demonstrated that the Th2 immune response is critical for the survival during acute *S. mansoni* infection [40, 41]. They concluded that the severity of the infection in the knockout mice was due to an increase in the TNF-α and NO levels.
However, when mice are persistently infected, the chronic Th2 response becomes highly harmful contributing to the development of hepatic fibrosis and portal hypertension [42, 43]. In addition, the Th2 response was also associated with the accumulation of a large number of arginase-1 expressing macrophages in and around the granulomas [42] and arginase-1 expressing macrophages in peritoneal cavity and increased circulating polyamines [44]. The presence of arginase-1 expressing macrophages was originally hypothesized to be involved in promoting the collagen deposit and the biosis hepatic through proline synthesis mediated by arginase-1 [25]. However, Herbert and colleagues demonstrated later using mice deficient in AaMφ (Il4ra−/−/LysMcre) that the alternative macrophage activation is essential for survival during schistosomiasis and down modulates T helper 1 responses and immunopathology [45]. Moreover, the development of Th2-driven fibrosis in those mice S. mansoni infected appears normal [45]. Recently, it was demonstrated that macrophage-specific arginase-1 exhibits both anti-inflammatory and antifibrotic activities during Th2-driven inflammatory responses induced by S. mansoni [46]. The authors demonstrated that, instead of promoting Th2-disease, macrophage-specific arginase-1 contributes to the resolution of schistosomiasis by inhibiting CD4+ T cell effector function [46]. The data showed by Pesce and colleagues identify arginase-1-expressing macrophage as critical mediators of immune down-modulation in chronic schistosomiasis [46]. Additionally, it has been also recently demonstrated that the resistin-like molecule (RELM)α, which is another molecule expressed by AaMφ, is also involved in the Th2 cytokine-down modulation during the pulmonary inflammation observed in schistosomiasis [47].

On the other hand, infection of mice with the natural mouse gastrointestinal helminth parasite Heligmosomoides polygyrus triggers a highly polarized Th2 response. Memory CD4+ T cells rapidly accumulate at the host-parasite interface and secrete IL-4, inducing localized development of AaMφs recruited to this site. These macrophages impair larval parasite health and mobility through an arginase-dependent pathway, contributing to eventual expulsion of adult worms [48]. It has been demonstrated that Th2 responses enhance gut contractility and luminal fluid secretion, leading to worm expulsion [49, 50]. Furthermore, specific inhibition of arginase activity during the infection with intestinal nematode parasite Nippostrongylus brasiliensis interfered with smooth muscle contractility and affected partially the protective immunity of the host [51]. Therefore, arginase-1 expressing macrophages are widely induced by helminths and they play different roles in those infections.

4. Arginase in Protozoan Infections

The type 1 pro-inflammatory response, crucial for parasite control during the acute phase of infection with protozoan parasites, should be carefully balanced by anti-inflammatory molecules like IL-10 and TGF-β to avoid excessive collateral damage to host tissues and cells. However, in many cases protozoan parasites take advantage of this anti-inflammatory response to persist in the host. It has been reported that during Trypanosoma brucei infection, sustained CaMφs could induce tissue damage, therefore mice that progress to a chronic stage, generate a Th2 response, able to favor the development of AaMφ [52]. In addition, it has been observed that Leishmania major has the ability to inhibit the production of IL-12 through the induction of IL-10 and TGF-β [53]. This imbalance underlies a shift from a Th1 to a Th2 immune response and reflects the susceptibility to the disease. This environment generates AaMφ facilitating the dissemination of the parasite in the host [54, 55]. Macrophage-IL-4 treatment previous to the infection with Leishmania major or Leishmania infantum biases the metabolism of L-arginine through arginase-1 towards the synthesis of polyamines, which promote the intracellular growth of the parasite [56]. Also, macrophage arginase-1-inhibition reduced the growth of the parasites due to an increase in NO production [56]. Additionally, in a mouse model of L. major infection, arginase-1 is induced in both susceptible and resistant mice during the development of the disease. The induction of the host arginase-1 in both strains is mediated by the balance between IL-4 and IL-12 and opposite to iNOS expression. Moreover, inhibition of arginase-1 reduces the number of parasites and delays disease outcome in susceptible mice, while treatment with L-ornithine increases the susceptibility of the resistant mice [54]. Furthermore, Kropf and colleagues also demonstrated that arginase-1 activity and production of polyamines are key factors in the regulation of leishmaniasis [55]. Moreover, another indication for the contribution of AaMφ to Leishmania susceptibility was demonstrated using macrophage/neutrophil-specific IL-4Ra-deficient mice. Those mice showed a significantly delayed disease progression with normal Th2 and type 2 antibody responses but improved macrophage leishmanicidal effector functions and reduced arginase-1 activity [57]. Therefore, arginase-1 induction could be considered a marker of disease in leishmaniasis.

On the other hand, a Th1 immune response, involving IL-12, IL-18, and IFN-γ as well as NO-producing CaMφ, favors the control of the early Trypanosoma cruzi infection that causes Chagas disease [58, 59]. However, if uncontrolled, the Th1 immune response causes pathology. In this respect, IL-4 and IL-10 have been implicated in resistance to T. cruzi by balancing the early stage proinflammatory immune environment [60, 61]. Therefore, once again, the Th2 environment could induce AaMφs and favor the installation of the parasite in the host. Arginase-1 activity, nevertheless, has not been necessarily induced by IL-4 during T. cruzi infection. We have demonstrated arginase-1 induction by the parasite component, cruzipain [62, 63]. We have showed that mice immunization with the immunodominant antigen cruzipain results in high Th2 cytokine secretion (IL-4, IL-5, IL-10), and marginal levels of IFN-γ and IL-12 [62]. In addition, cruzipain-stimulated macrophages exhibit increased arginase-1 activity and expression, and secrete IL-10 and TGF-β [63, 64]. Moreover, cruzipain-activated macrophages favor T. cruzi growth at the same extend as was observed in IL-4-treated macrophages [63] and arginase-1 inhibition leads to a drastic reduction in T. cruzi replication.
5. Alternative Activation Markers in Human and Murine Macrophages

AaMφ generation is associated with changes in macrophage function and distinctive gene signatures. Although the alternative activation markers for human and murine macrophages have long been considered analogous, there are differences between species. IL-4 and IL-13 induce genes conserved in both species such as MHC-II, MR, MGL1/2, and CD23 as well as divergent ones such as arginase-1, chitinase-like molecules (Ym1/2), and RELMα in mouse, and AaMφs might favor the onset of a chronic infection during Chagas disease.

6. Role of Arginase-1 in Immunosuppression

The ability of arginase-1-expressing macrophages to suppress T cell proliferation could explain their presence in placenta and lung of healthy individuals [8, 75]. However, the presence of suppressive arginase-1 expressing macrophages during infections as well as during cancer could be detrimental for the host [76].

As was mentioned above, during Brugia malayi experimental infection, it has been demonstrated that IL-4-dependent macrophages recruited in vivo actively suppress the proliferation of lymphocytes. These macrophages block proliferation by cell-to-cell contact, implicating a receptor-mediated mechanism. [37]. In addition, it was also recently demonstrated that arginase-1 plays an essential role in the T cell suppression observed at the site of pathology in non-healing leishmaniasis lesions [77]. Modollel and colleagues demonstrated that arginase-1 is highly expressed at the site of pathology in nonhealing lesions and causes local depletion of L-arginine which impairs the capacity of T cells in the lesion to proliferate and to produce IFN-γ, required for parasite killing. They clearly showed that arginase-1 is mediating T-cell immunosuppression since its inhibition or the injection of L-arginine reverses suppression and results in macrophage efficient control of parasite replication [77]. However, during schistosomiasis, macrophage-specific arginase-1 contributes to the resolution of the infection by inhibiting CD4+ T cell proliferation and cytokine production. The authors showed that arginase depletion by arginase-1 expressing macrophages was the primary suppressive mechanism while no significant contribution for IL-10 or TGF-β was observed in these studies [46]. Moreover, Terrazas and colleagues have showed that Taenia crassiceps-induced macrophages have suppressive T cell activity and this effect was IL-10, IFN-γ, NO independent, and cell-cell contact dependent [36]. Taenia crassiceps-induced macrophages showed an alternative activated profile with high expression of Fizz1, Ym1, and arginase-1 [36]. The authors demonstrated that the suppressive ability of the Taenia crassiceps-induced macrophages involves programmed death ligand molecules, PD-L1 and PD-L2, which were found to be upregulated in those macrophages [36]. These molecules bind to the receptor programmed death 1 (PD-1) which is expressed on activated T cells (B cells and myeloid cells also) and their interactions result in down-modulation of T cell responses [78, 79]. In addition, the selective upregulation of PD-L1 on macrophages by Schistosoma mansoni worms has shown to induce anergy of T cells during early acute stages of infection.
before the subsequent emergence of egg-induced T cell suppression in the chronic stages of infection [80]. Studies in progress in our group demonstrated that the PD-1/PD-L pathway may be also involved in the immunosuppression observed during the acute phase of T. cruzi infection [81]. We observed change in the expression of these molecules during the acute phase of T. cruzi infection in CD3+, CD11c+, and F4/80+ peritoneal cells. In addition, T. cruzi macrophages were able to suppress concanavalin A (ConA) T cell induced proliferation which is restored by blocking PD-1 pathway with antibodies or by inhibiting arginase-1 activity. In addition, our preliminary data suggest that PD-L2 could be involved in arginase-1 induction in T. cruzi infected macrophages (Dulgerian et al. unpublished data). Therefore, this may suggest that PD-1-PD-Ls interaction is important in arginase-1 modulation and in T. cruzi replication in macrophages.

In this context, it has been recently showed that the activity and expression of arginase-1 could be regulated by both PD-1 and CTLA-4 on the myeloid-derived suppressor cells (MDSCs) [82]. It has been extensively demonstrated that increased metabolism of L-arginine by myeloid cells can result in the impairment of lymphocyte responses to antigen during immune responses and tumor growth [76]. PD-1 molecules expressed on MDSCs can be involved in the regulation of MDSC function by regulating the activation and expression of arginase-1. The regulation of arginase-1 activity and expression by costimulatory or co-inhibitory molecules on the MDSCs might be important in inducing and maintaining immunosuppression [76].

On the other hand, the role of human granulocyte arginase in immunosuppression was explored by Munder and colleagues [74]. They demonstrated that upon human polymorphonuclear granulocytes (PMN) cell death, arginase is liberated and very high activities of this enzyme accumulate extracellularly during purulent inflammatory reactions. PMN arginase induces a profound suppression of T cell proliferation and cytokine synthesis. This T cell suppression is due to arginase-mediated depletion of L-arginine in the T cell environment, which leads to CD3ζ chain down-regulation [74]. Recently they showed that PMN arginase-mediated suppression reach also NK cells [83]. Granulocyte arginase severely impairs NK cell proliferation and IL-12/IL-18-induced secretion of IFN-γ [83].

8. Concluding Remarks

The diversity of macrophage activation states is probably as diverse as the number of environmental conditions to provide the appropriate immune response. It is influenced by the complexity of the stimulus, the sequence of exposure, and the status of macrophage differentiation at the time of exposure. In this review we have focused our discussion on the role of arginase-1-containing macrophages in parasitic infections. The outcome of protozoan infections is crucially dependent on the order, timing, and relative strength of type 1 versus type 2 responses and CaMφ versus AaMφ generation (Figure 1). During several infections induction of arginase-1 macrophages was showed to have a detrimental role by limiting CaMφ-dependent parasite clearance and promoting parasite proliferation. Additionally, the role of arginase in T-cell suppression has been explored recently. During several infections, arginase-1 T cell suppression contributes to failure to eliminate the pathogen. However, during schistosomiasis arginase-1-expressing macrophages suppress Th2-dependent inflammation and fibrosis, contributing to the resolution of the infection. Arginase suppressive activity has been mainly associated with L-arginine depletion leading to CD3 instability. In addition, PD-1 and their ligands have been also involved in arginase-1 suppression (Figure 2). On the other hand, although arginase-1 induction is confined mainly to murine macrophages, it was demonstrated that it is expressed constitutively in human granulocytes and it showed some similar function to the murine arginase (Figure 2). However, although the general functions and behaviors of murine and human AaMφs are thought to be preserved, human alternative activated macrophages should be further investigated.

Additionally, recent findings have improved the understanding of signals involved in arginase-1 expression. In addition to the well-known role of STAT-6 in IL-4 and IL-13-arginase induction, during Th1 responses, a novel TLR dependent but STAT6-independent pathway of arginase-1 expression was identified.

7. Signals Involved in Arginase-1 Induction

One of the first works that investigated the intracellular signals involved in arginase induction by LPS showed that protein kinase A (PKA) activation was required whereas the activation of the enzyme did not depend on PKC, neither the intracellular levels of Ca++ [84]. Later, the signals involved in IL-13 arginase-1 induction were studied by Chang and colleagues [85]. They demonstrated that IL-13 down-regulates NO production through arginase induction via cAMP/PKA, tyrosine kinase (TK), and p38 MAPK signaling [85]. Recently findings correlate with the previous role of PKA in arginase induction in macrophages [86]. We have previously shown that arginase-1 induction mediated by cruzipain involves the activation of multiple intracellular signals such as TK, PKA, and p38 MAPK [64, 87], similar to the signals triggered by IL-13 [85]. Furthermore, it was demonstrated that the transcription factor STAT-6 is required for arginase-1 induction in IL-4 and IL-13-treated macrophages [88, 89]. However, it was recently shown that some intracellular pathogens induced arginase-1 expression in mouse macrophages through the Toll Like Receptor (TLR) pathway [90]. In contrast to diseases dominated by Th2 responses in which arginase-1 expression is greatly increased by IL-4 and IL-13 signaling through the transcription factor STAT6, TLR-mediated arginase-1 induction was independent of the STAT6 pathway. Specific elimination of arginase-1 in macrophage favored host survival during Toxoplasma gondii infection and decreased lung bacterial load during tuberculosis infection. Therefore, TLR pathway could be also advantageous to certain pathogens [90].
**Figure 1:** Role of macrophage activation in parasitic infections. A type 1 cytokine-dependent proinflammatory response inducing classically activated macrophages (CaMφs) leads to NO production and also to the synthesis of several products of NO reaction. CaMφs are crucial for parasite control during protozoan infections but can also contribute to the development of immunopathological disease symptoms. Type 2 cytokines such as IL-4 and IL-13 antagonize CaMφs inducing alternatively activated macrophages (AaMφs) that upregulate arginase-1 expression. Arginase-1 can also be induced during the infection by apoptotic cells or even directly by parasites or parasite components. Arginase-1 limits CaMφ-dependent parasite clearance promoting parasite proliferation. Additionally, arginase-1 suppresses T cell response. Therefore, generation of alternative activation states of macrophages could limit collateral tissue damage because of excessive type 1 inflammation. However, they affect disease outcome by promoting parasite survival and proliferation.

**Figure 2:** Role of arginase in immunosuppression. During parasitic infections, mouse macrophage-specific arginase-1 induces T cell suppression due to arginase-mediated depletion of L-arginine in the T cell environment, which leads to CD3ζ chain down-regulation. Additionally, PD-1/PD-1 pathway may be also involved in the T cell suppression. Furthermore, human granulocyte arginase can also induce immunosuppression by a similar mechanism. Upon human polymorphonuclear granulocytes (PMN) cell death, arginase is liberated and high activities of this enzyme accumulate extracellularly during purulent inflammatory reactions. PMN arginase induces a profound suppression of T cell and NK cell proliferation and cytokine synthesis.
Finally, our knowledge of how different types of macrophages affect the course of infectious diseases caused by protozoan parasites should provide therapeutic benefits in controlling these infections.

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