Macrophage Migration Inhibitory Factor (MIF): A Key Player in Protozoan Infections

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Abstract

Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine produced by the pituitary gland and multiple cell types, including macrophages (Mø), dendritic cells (DC) and T-cells. Upon release, MIF modulates the expression of several inflammatory molecules, such as TNF-α, nitric oxide and cyclooxygenase 2 (COX-2). These important MIF characteristics have prompted investigators to study its role in parasite infections. Several reports have demonstrated that MIF plays either a protective or deleterious role in the immune response to different pathogens. Here, we review the role of MIF in the host defense response to some important protozoan infections.

Key words: Macrophage migration inhibitory factor; Protozoan infections; Inflammatory response; Control of parasite infections; innate immune response.

Introduction

MIF was originally discovered (in 1966) as a lymphokine, derived from activated T-cells, that inhibited the random migration of macrophages in vitro and was shown to be involved in the mechanism of delayed-type hypersensitivity [1, 2]. Currently, it is known that MIF is a widely expressed and pleiotropic cytokine that functions as a critical upstream mediator of innate immunity and promotes numerous pathophysiological processes [3-11], such as glomerulonephritis [12, 13], arthritis [5, 14], experimental autoimmune encephalomyelitis (EAE) [15], experimental autoimmune myocarditis (EAM) [16], gram-negative [17-23] and gram-positive sepsis [23, 24], colitis [10, 25], asthma [8] diabetes, and pancreatitis [26-28]. MIF is produced and secreted primarily by immune cells, such as lymphocytes, Mø, DC, neutrophils and pituitary cells [29, 30]. MIF secretion is tightly regulated by stress and immune stimuli, including endotoxins, inflammatory cytokines (interferon (IFN)-γ, tumor necrosis factor (TNF)-α) and glucocorticoids [29, 31-33]. Once secreted, MIF exhibits a broad range of immune and inflammatory activities, including the induction of inflammatory cytokines such as TNF-α, IFN-γ, interleukin (IL)-1β, IL-12, IL-6 and, CXCL8 (also known as IL-8), among others [20, 32, 34-40]. MIF favors the expression of the Toll-like receptor 4 (TLR4) gene, which encodes the signal-transducing element of the lipopolysaccharide (LPS) receptor complex [24, 41, 42] through the activation of transcription factors of the ETS family [43]. In addition, MIF counter-regulates the immunosuppressive effects of glucocorticoids [32, 44-46], and it sustains macrophage proinflammatory functions by inhibiting p53 [47]. MIF also promotes the migration and recruitment of immune cells inducing the expression of chemokines (monocyte chemoattractant protein
(MCP)-1, and adhesion molecules as intercellular adhesion molecule (I-CAM)-1 and vascular cell adhesion molecule (V-CAM)-1 [48-51].

Parasitic infections are important cause of morbidity and mortality in humans, and the innate and adaptive immune responses triggered by these organisms are critical in determining their outcome. Parasitic-associated factors and host-derived components are also important inflammatory modulators. Recognition of these molecules triggers signaling pathways that influence the host-response to infection and disease progression. In this context, MIF is the role of MIF in the immune response to parasitic infections has only recently been elucidated, providing valuable information that must to be clarified. The aim of this review is to provide an overview of the current literature regarding the role of MIF in important protozoan infections. We will focus on immune response modulation, the implications of such modulation and the possible mechanisms involved.

We will also discuss the differences and similarities in MIF activity infections caused by distinct parasites.

**Malaria**

Malaria is caused by intracelluar parasitic protozoa of the genus *Plasmodium* (*P*) and is transmitted by the infected female *Anopheles* mosquito during blood meals. Malaria is a major cause of severe illness and death in many part of the world. It causes 300 to 500 million new infections per year resulting in approximately 1 to 2 million deaths, and these primarily occur in children under the age of 5 years. Severe anemia and cerebral malaria are the major complications leading to malaria-induced morbidity and mortality [52]. Factors such as host genetic variation, age of first exposure, rate of exposure (endemicity) [53, 54] and the host immune response to *P. falciparum* [55] play an important role in the generation of symptoms and disease [56, 57].

Remarkable research on the role of MIF in malaria has been recently conducted (Table 1).

**Table 1. MIF in Malaria infection**

| Parasite | Model | Disease | in vitro/ in vivo | Treatment | Properties | MIF role | Ref. |
|----------|-------|---------|------------------|-----------|-----------|----------|------|
| *P. chabaudi* | BALB/c mice | SMA | in vitro | rMIF+ Epo | ↑Parasitemia | Causes erythropoiesis suppression and SMA development | [58] |
|           | BALB/c mice | SMA | in vitro | rMIF+IFN-γ; TNF-α+Epo | ↑Parasitemia↑MIF↑SMA | Suppressed erythropoietin colony formation and synergized with TNF-α and IFN-γ modulating MAPK activation. | [60] |
| *P. chabaudi* | MIF-KO BALB/c mice | SMA | in vivo | | ↑Parasitemia↑Mortality↑BFU↑CFU | | |
| *P. chabaudi* | MIF-KO BALB/c mice | Malaria | In vivo | | | MIF modulates the balance between Th1 and Th2 effector responses, by attenuating the development of Th1 responses, inducing anti-inflammatory cytokines during the infection of *P. c. adami*. | [59] |
| *P. vivax* | Adults Adolescents Children | Acute malaria uncomplicated | in vivo | | ↑MIF, TNF-α, IFN-γ, IL-12, MCP-1 and IL-10↑GM-CSF↑Hb and ↑MIF | Enhancing the Ab production against the parasite which cause erythrocyte lysis | [62] |
| *P. falciparum* | Zambian children | Malaria | in vivo | | ↑MIF peripheral blood | Promote polymorphisms, modulate the immune response to hemozoin | [60] |
| Pregnant woman | Placental malaria | in vivo | | | ↑MIF from Mo with 5-CATT (low repeat)↑MIF from Mo 6/7 CATT↑MIF in IVB↑MIF in peripheral and cord | Enhancing the local immune response | [63] |
in vivo | Plasma MIF in placental plasma ↑IL-12 IL-18 TGF-β1 Enhancing immune response [64]
---|---|---|---|---|---
in vitro | MIF in PBMC ↑MIF in IVB cells [65]
---|---|---|---|---|---
in vivo | Plasma MIF in non-survivors ↓Plasma MIF in patients with mild malaria Protective role in CM and induce fatal complications [61]
---|---|---|---|---|---
Indian adults | Cerebral malaria in vivo | Plasma MIF in PBMC ↑MIF in amniotic epithelium and IVBMC ↑MIF in villous stroma and extravillous trophoblast [65]
---|---|---|---|---|---
Adults Adolescents | Acute infec. malaria un-complicated in vivo | MIF, TNF-α, IFN-γ and MCP-1↑ in peripheral blood ↑IgM and IgG against parasite correlated to ↓Hb conc. Enhancing the Ab against parasite which may cause erythrocyte lysis [62]
---|---|---|---|---|---
Malawian Children | Cerebral malaria in vivo | MIF in cerebral vascular walls skeletal muscle and chest Absence of MIF have a survival advantage in preventing intracranial hemorrhage in systemic infections [66]
---|---|---|---|---|---
Gabonese children | Acute malaria in vivo | MIF mRNA in peripheral blood PG62 and TGF-β1↑ parasitemia ↑IFN-γ, TNF-α, INOS and IL-10 Reduced MIF and TGF-β1 promote an ineffective immune response that enhanced pathogenesis [67]
---|---|---|---|---|---
Kenyan children | SMA in vivo | MIF mRNA in PBL ↑% PCM related to ↑SMA and ↓MIF in PBMC A protective response against severe disease [68]
---|---|---|---|---|---
Caucasian Adults | Acute malaria in vivo | Plasma MIF ↑Peripheral lymphocytes ↓Parasitemia Hb unchanged Reallocation of lymphocytes to tissues during acute malaria explains the decline in circulating lymphocytes that may causes MIF↑ in plasma [69]
---|---|---|---|---|---
Zambian children | malaria in vivo | 6,7 and 8 CATT repeats at MIF-794 allele are correlated to ↑Parasitemia ↑CATT repeat at MIF-794 allele is correlated to ↓Parasitemia Protective effect of MIF-794, 5 CATT allele [81]
---|---|---|---|---|---
Kenyan children | Acute malaria in vivo | ↑risk of developing HDP of C/C compared to G/G genotype MIF-173 G/C C/C genotypes are associated with an increased risk of HDP, ↑plasma MIF but not increased SMA susceptibility [82]
---|---|---|---|---|---
In vitro | pfHz or sfHz | MIF in PBMC [83]
---|---|---|---|---|---
Kenyan children | SMA in vivo | pfHz MIF in PBMC with MIF-173 G/G genotype compared to G/C genotype MIF promoter at the -173 and -794 polymorphisms can both confer protection or susceptibil to SMA, Carriers of the disease associated alleles have decreased periph-erical blood MIF [83]
---|---|---|---|---|---

Erythroid (BFU-E), multipotential (CFU-GEMM), and granulocyte-macrophage (CFU-GM) progenitor-derived colony formation. erythropoietin (Epo); Monocytes (Mo); Intervillous blood (IVB); Peripheral bone marrow cell (PBMC); Peripheral blood lymphocytes (PBL); Pigment containing monocytes (PCM); Mononuclear intravillous cells (IVBMC); High density parasitemia (HDP); P. falciparum hemozoin (pfHz); Sintetic Hemozoin (sHz); Severe Malaria Anemia (SMA); Cerebral malaria (CM).

In one study, Martiney et al. reported that the ingestion of P. chabaudi-infected erythrocytes or malarial pigment (hemozoin) by macrophages induces the release of MIF, resulting in high circulating levels of MIF in the sera and bone marrow of P. chabaudi-infected BALB/c mice. Furthermore, recombinant MIF administration suppressed the erythroid and other myeloid progenitor development in the presence of erythropoietin an erythropoiesis inhibitory role for MIF [58]. These findings were supported later in vitro studies in which the combined subinhibitory concentrations of MIF, TNF-α and IFN-γ acted synergistically to inhibit erythroid differentiation and hemoglobin production by antagonizing the pattern of
mitogen-activated protein (MAP) kinase phosphorylation that normally occurs during erythroid progenitor differentiation. An in vivo study, using P. chabaudi-infected MIF knockout (KO) mice, showed that the absence of MIF is related to an increase in erythropoiesis and decreased mortality. Correlated with a recent study by Malu DT et al, where MIF KO mice showed increased resistance to P. chabaudi adami infection associated with enhanced IFN-γ and reduce IL-4 and IL-10 production by CD4+ T cells, suggesting a regulatory role for MIF on T cell activation, which favors a Th2 type susceptible response in WT mice [59]. In addition, increased MIF circulating levels found in Zambian children supports the hypothesis that Plasmodium infection is a potent stimulus for systemic MIF expression in humans, which may be involved in the pathophysiology of malaria-induced anemia [60].

Recent research regarding the role of MIF in the pathogenesis and outcome of cerebral malaria showed that patients with mild malaria and survivors of cerebral malaria had low peripheral blood MIF levels compared to cerebral malaria non-survivors, suggesting that elevated MIF levels may be a risk factor for mortality in cerebral malaria patients [61]. Moreover, patients with P. falciparum and P. vivax infections showed significant increases in MIF, TNF-α, IFN-γ, IL-12, IgM and MCP-1 in the peripheral blood. Also high IgM antibody levels against stage parasite forms were associated with low hemoglobin (Hb) and increased MIF levels, indicating that MIF participates in the inflammatory immune response to malaria. This response, in concert with other inflammatory cytokines and the production of specific antibodies against the parasite, may lead to pathologic responses [62]. However, MIF does not always act systemically. Previous studies by Chaisavaneeyakorn et al reported significantly elevated MIF levels in the inter-villous blood (IVB) plasma in pregnant women with placental malaria compared to both peripheral plasma and cord plasma [63]. Similar results were obtained by Chaiyaroj et al, who observed significantly higher MIF production by inter-villous blood mononuclear cells (IVBMC) compared to peripheral blood mononuclear cells (PBMC), as well as high MIF levels in placental plasma compared to paired peripheral plasma [64]. These data were confirmed by immunohistological studies in term placentas, demonstrating that, although MIF is expressed in various cellular compartments, enhanced MIF expression occurs specifically in mononuclear cells and amniotic epithelial cells in placental malaria [65]. These data indicate that increased MIF levels in infected placentas may play an important role in the local immune response, possibly through macrophage activation for parasite clearance. However, not all reports show local or systemic MIF overexpression. Immunohistological studies have reported that, although MIF was found in the nuclei of skeletal muscle cells, it was not found in the cerebral vascular walls of cerebral malaria patients. The lack of MIF overexpression in the cerebral vasculature may prevent excessive cerebral perfusion pressure and the risk of intracranial hemorrhage during systemic inflammation. Interestingly, the role of MIF in nuclei has not yet been determined [66]. Moreover, research in Gabonese children with acute malaria has shown significantly low MIF mRNA levels in PBMCs and low MIF protein levels in peripheral blood, which was associated with low levels of TGF-β1 in presence of TNF-α, IFN-γ, and inducible nitric oxide synthase (iNOS). These results suggest that the reduction of transforming growth factor beta (TGF-β1) and MIF in children with acute malaria may promote an ineffective immune response culminating in enhanced pathogenesis [67]. These findings are consistent with a later study in 357 Kenyan children, which showed that malaria-induced anemia was associated with decreased circulating MIF levels. The authors also showed low MIF expression in peripheral blood lymphocytes (PBL), peripheral blood mononuclear cells (PBMCs), and in a high percentage of pigment containing monocytes (PCM), concluding that the effective production of MIF during childhood anemia may be protective against severe disease [68] (Fig 1). In addition a recent study in 10 healthy volunteers infected with P. falciparum, showed that a decrease in systemic MIF levels during acute infection is associated with a decline in circulating lymphocytes. Because T cells are the primary source of circulating MIF, these results may be attributed to the reallocation of lymphocytes from the peripheral plasma to infected tissues leading to a decrease in circulating MIF levels [69].

Although much research has been conducted in humans, the role of MIF in malaria remains unclear partly due to genetic variability, as malaria has exerted selective pressure on the human genome [70]. Interestingly, some studies have attributed the variations in MIF circulating levels and susceptibility to severe malaria-induced anemia to the tetranucleotide short tandem repeat polymorphism (STRP) MIF-794 CATT and the single nucleotide polymorphism (SNP) MIF-173 G/C allele [8, 71-83]. The -173 C allele is commonly associated with elevated MIF expression and increased susceptibility to inflammatory diseases [71-75, 77, 78, 80], while longer CATT repeats (>5) at MIF-794 can cause increased susceptibility [80] and
irregular MIF production [74, 75, 79] in inflammatory diseases. Related to this, previous studies in Zambian children have shown that monocytes with longer CATT repeats (>5) were associated with high MIF production [60]. Subsequent studies in Zambian and Kenyan children demonstrated that carriers of longer (>5) CATT repeats at the MIF -794 allele and the CC genotype at the MIF -173 allele, were associated with increased susceptibility to high-density parasitemia [81, 82]. Recently, Awandare et al., in a study in Kenyan children, reported that the 7C and 8C MIF-794/-173 haplotypes and an increased number of CATT repeats (>5) in the MIF -794 allele were associated with increased susceptibility to severe malaria anemia (SMA) and a progressive decrease in circulating MIF concentrations. This group also discovered that the 6G haplotype and short CATT repeats were associated with decreased susceptibility to SMA and increased MIF production, suggesting that carriers of the disease-associated alleles may have decreased MIF levels in the blood [83]. Moreover, even though these findings indicate a high prevalence of the short 5/6, 7, and 8 CATT repeats at the -794 and -173 C alleles in Kenyan and Zambian children compared to Caucasians, which points to a selective pressure in these endemic regions by *P. falciparum*, further research will be necessary to clarify the inconsistencies in previous studies regarding MIF circulating levels and to show the clear involvement of MIF in either malaria resistance or pathology (Fig 2).

**Figure 1.** Overview about the role of MIF during *Plasmodium* infection. Theory 1. Mice infected with *plasmodium* (1) develop high MIF serum levels (2), MIF inhibits eritropoyesis (3) and promotes pathological complications increasing the risk of developing severe malaria anemia (SMA) (4). Plasmodium infected human could develop low (3A) or high levels (3B) of MIF, depending of the (MIF’s polymorphisms expressed). Low levels of MIF correlates with high density parasitemia (HDP) in blood but low risk of developing SMA (5A). However, high expression of MIF induces SMA (5B). Plasmodium infected pregnant woman develop high levels of MIF in placental plasma, amniotic epithelium, mononuclear intervillous blood (IVB), and mononuclear tervillous cells (MIVC). All together indicate that MIF is associated to inhibition of eritropoyesis and promoting SMA, however it is not crucial in the control of the infection.
Figure 2. Overview about the role of MIF during Plasmodium infection. Theory 2. Human infected with plasmodium (1) down regulates the expression of MIF in peripheral lymphocytes (2), depending of the expressed MIF’s polymorphisms it may favors several malaria anemia (SMA) (B and C). In line with these observations high levels of MIF prevent SMA (A, D). All together indicate that MIF has a protective role against plasmodium infection and low levels of MIF increase the risk of developing SMA.

Leishmaniasis

Leishmaniasis is caused by protozoan parasites belonging to the genus Leishmania and approximately 350 million men, women and children in 88 countries are in danger of contracting the disease. As many as 12 million people may be currently infected, and an estimated 1–2 million new cases occur every year [84]. Generally, infection by these parasites can be divided into three main forms: cutaneous, mucocutaneous and visceral leishmanioses. The disease is prevalent in many tropical and subtropical regions of the world, where it is transmitted via the bite of an infected sandfly [85].

Previous reports have shown that MIF plays a critical role mediating host resistance to Leishmaniasis. Juttner et al. found in vitro that both recombinant murine or human MIF, at 1.5 and 2.5 μg/ml concentrations could activate macrophages to kill Leishmania major [86]. The use of anti-TNF-α antibody or TNF receptor p55-KO mice as well as L-NIL or iNOS-KO mice showed that leishmanicidal activity was mediated by TNF-α autocrine signaling and the production of nitric oxide metabolites by macrophages after MIF stimulation. Moreover, both susceptible BALB/c and resistant C57BL/6 mouse strains expressed high levels of MIF mRNA in lymph nodes draining the site of L. major infection. Related to this, in a study by Satoskar et al., experimental L. major infection in C57BL/6 MIF KO and wild-type (WT) mice showed that MIF KO mice were more susceptible to disease due to significantly larger lesions and greater parasite burdens than WT mice. However, similar proliferative responses and production of IL-4 and IFN-γ cytokines by lymph nodes were observed when stimulated in vitro with L. major antigen (LmAg). In addition, IFN-γ stimulated Mø from MIF KO mice had a defective leishmanicidal activity, which was associated with low superoxide and nitric oxide levels, and high IL-6 levels. This finding suggests that susceptibility of MIF KO mice to L. major infection is due to an impaired macrophage leishmanicidal activity rather than deregulation of Th1 and Th2 responses [87]. Furthermore, Xu et al. demonstrated that oral administration of attenuated Salmonella-transfected plasmids encoding the murine MIF gene and the TNF-α gene enhanced the resistance of BALB/c mice infected with L. major, and this resistance was associated with high iNOS expression compared to other plasmids encoding the MIF, TNF-α or IFN-γ genes alone. This indicates that MIF may play an important role in the resistance to leishmaniasis, likely by synergizing with other inflammatory cytokines, such as TNF-α via the induction of iNOS expression [88]. Interestingly, Kozaci et al. revealed that human patients with acute cutaneous leishmaniasis caused by L. tropica showed high MIF levels compared to healthy subjects [89].
Moreover, a recent study by Santos-Oliveira J.R. et al. in visceral leishmaniasis (VL) patients, the authors demonstrated that high LPS levels from a possible microbial translocation due to damage by visceral leishmaniasis (VL) was correlated with increased pro-inflammatory cytokines (MIF, IFN-γ, TNF-α, IL-2, IL-6, IL-12, IL-17) and low numbers of CD4+ and CD8+ T cells, suggesting a strong lymphocyte activation by the proinflammatory cytokine storm that lead to lymphocyte death by apoptosis, therefore MIF may contribute in the immuno-pathogenesis by LPS stimulation during VL [90]. In addition, a clinical study by Bimal et al. reported that CD2+ T-cells isolated from patients with active visceral leishmaniasis (VL) produced high levels of MIF after anti-CD25 stimulation in vitro. Moreover, after anti-leishmanicidal treatment, patients with VL showed higher numbers of CD2+ T-cells, indicating a possible role for CD2+ T cells and MIF in the immune response to VL [91]. Related to this, Kar, Metz, and McMahon-Pratt discovered that P-4 antigen-vaccinated BALB/c mice presented without lesions or detectable parasites after *Leishmania pifanoi* infection. This protection was shown to be CD4+ T cell-dependent and lead to the production of MIF, TNF-α and IFN-γ, but not IL-4. Moreover, the addition of antibodies against either MIF, TNF-α or IFN-γ separately or simultaneously, to macrophages from P-4-immunized mice in vitro, decreased leishmanicidal activity, suggesting that MIF potentially contributes to the control of *L. pifanoi* infection in P-4-vaccinated mice [92]. Together, these findings demonstrate a crucial role for MIF in the cellular immune response against leishmaniasis. MIF appears to be capable of killing *Leishmania* parasites by acting directly or indirectly with other cytokines, such as TNF-α and reactive products like nitric oxide. However, additional human studies are needed to confirm this data and, more importantly, to elucidate the molecular mechanisms of how MIF induces its leishmanicidal activity.

### Table 2. MIF in Leishmaniosis

| Parasite               | Model                   | Disease | in vitro/ in vivo | Treatment | Properties | MIF role | Ref. |
|------------------------|-------------------------|---------|------------------|-----------|------------|----------|------|
| *L. major*             | BALB/c mice             | CL      | in vitro         | rhMIF     | ↑Infected Mø | Induces a leishmanicidal activity in MO mediated by TNF-α and NO | [86] |
|                        | C57/BL/6 mice           | CL      | in vitro         | mrmIF, anti-TNF-α, TNF-α KO, TGF-β1, IL-13, IL-10 + rMIF | ↑TNF-α by PECS | Mediate *L. major* killing in Mø | |
|                        | p55-KO iNOS KO          |         |                  | MIF + IFN-γ | ↑NO by Mø | Mediated leishmanicidal function | |
|                        | BALB/c mice             | CL      | in vivo          | IFN-γ     | ↑leishmanicidal activity | | |
|                        | C57/BL/6 MIF-KO mice    | CL      | in vitro         | IFN-γ     | ↑NO and ↑IL-6 by Mø | | |
|                        | BALB/c mice             | CL      | in vivo          | Oral *S. typhimurium* transfected with plasmid encoding IFN-γ or MIF | ↑MIF in lymph node cells | | |
| *L. tropica*           | Healthy Subjects (HS)   | CL      | in vivo          | IFN-γ     | ↑MIF in serum | Favors cellular immune response | [89] |
| *Leishmania infantum*  | Human                   | Viseral | In vivo          | IFN-γ, TNF-α, IL-2, IL-6, | ↑LPS levels in plasma correlated to ↑MIF, IL-6, ↑IL-8, ↑FFABP levels, ↑sCD14, ↑% of TCD3 HLA-DR and ↑% of CD4+ CD25+ compared to Healthy Subjects (HS) | MIF production may contribute to the inflammatory response in VL patients, and the increased susceptibility to the immunopathogenesis caused by LPS stimulation. | [90] |
Trypanosomiasis

Trypanosomiasis is caused by protozoan parasites of the genus Trypanosoma. The two major diseases caused by these organisms are sleeping sickness in Africa and Chagas disease in America. Chagas disease is a zoonosis (or an anthropozoonosis) caused by the flagellated protozoan parasite Trypanosoma cruzi. It is transmitted to man by the infected feces of a blood-sucking triatome bug through the insect sting. An estimated 18 million people are infected worldwide, and most cases occur in Latin America, where Chagas disease is endemic. More than 100 million people are at risk of contracting the disease [93]. Sleeping sickness is a parasitic disease transmitted by the bite of the ‘Glossina’ insect, commonly known as the tsetse fly. This disease threatens more than 55 million people in 36 countries with an estimated 300,000 new cases per year in Africa alone [94].

There are few, but notable, papers regarding the role of MIF in trypanosomiasis. Our group has found that infected (Trypanosoma cruzi or the Queretaro strain) MIF KO mice displayed high levels of blood and tissue parasitemia, which was associated with severe heart and skeletal muscle immunopathology. Inflamed hearts from T. cruzi-infected MIF KO mice showed high amastigotes nests and expressed high IFN-γ transcripts, but fewer IL-12, p35, IL-12, p40, IL-23 and iNOS transcripts. Further, these mice succumbed to T. cruzi infection faster than WT mice. This enhanced susceptibility in MIF KO mice was associated with an important reduction of pro-inflammatory cytokines in the sera during early infection. TNF-α, IL-12, IL-18, IFN-γ and IL-1β levels correlated with the impaired spleen cell production of pro-inflammatory IL-12 and IFN-γ, but anti-inflammatory IL-4 and IL-10 cytokine levels were not elevated, demonstrating that the increased susceptibility was not due to high production of anti-inflammatory cytokines. Therefore, MIF may be required for the optimal activation of host innate responses by up-regulating inflammatory cytokines that are crucial for resistance to T. cruzi infection [95]. In relation to this, a recent study by Nishimura K et al reported that MIF, GM-CSF, IL-12 and TNF mRNA are highly expressed in spleen macrophages during Trypanosoma brucei brucei (ILS) infection, in contrast to Trypanosoma gambiense welcome strain (WS) infection, the authors explained that this difference may be due to a possible macrophage activation during ILS infection and a macrophage immunosuppression during WS infection, probably by differences in characteristics between WS and ILS, these findings indicate that MIF is involved in the inflammatory immune response against Trypanosomiasis and this involvement may depend on the parasite strain [96]. Additionally, Paiva et al. reported a lethal synergism between T. cruzi infection and LPS-induced shock, where MIF and TNF-α play an important role. Briefly, BALB/c mice infected with the T. cruzi Y strain after an LPS injection showed enhanced susceptibility to endotoxemia. This was in contrast to TNF KO mice treated with anti-MIF, indicating that increased susceptibility to endotoxemia is due to T. cruzi induced MIF and TNF-α, suggesting again that MIF may act synergistically with the TNF pathway to induce
pro-inflammatory responses during early infection [97]. Interestingly, hearts and skeletal muscle from infected mice (RA T. cruzi strain) showed early MIF mRNA induction, which was accompanied by enhanced transcripts for cytokines, chemokines and chemokine receptors, such as TNF-α, IFN-γ, CCL5, CXCL9, CCR5, CXCR3 and iNOS. These results lead to the consideration of MIF as part of the primary response against this parasite, and that it acts by collaborating with other cytokines and chemokines in the inflammation processes of infected organs and tissues [98]. In addition, a recent study reported that, in T. brucei infected C57BL/6 mice, MIF, together with important chemokines (CXCL9, 10, CCL2, 3, 4, and 5 mRNA), are significantly induced during the first, and important, peak of parasitemia and the highest expansion of CD11b+Ly6C+ monocytic cells in the liver. However, studies in MIF KO infected mice showed that the egression of CD11b + Ly6C + monocytes from the bone marrow to the blood is MIF-independent, but CCR2-dependent, indicating that MIF does not participate in monocyte recruitment. However, it may be possible that the early induction of MIF in the liver better regulates inflammatory cytokine production. Together, these studies designate an important role for MIF in the induction of a resistant innate immune response to T. cruzi infection. Clinical studies in humans will be necessary to confirm these data [99].

Table 3. MIF in Trypanosomiasis

| Parasite | Model | Disease | in vitro/ in vivo | Treatment | Properties | MIF role | Ref. |
|----------|-------|---------|------------------|-----------|------------|----------|------|
| T. cruzi Ninoa | WT MIF-KO BALB/c mice | Acute trypanosomiasis | in vivo | ↑parasitemia | Activation of innate immunity, inducing inflammatory cytokines | [95] |
| T. cruzi Queretaro | WT MIF-KO BALB/c mice | Acute trypanosomiasis | in vivo | ↑parasitemia | Activation of innate immunity, inducing inflammatory cytokines | [95] |
| T. brucei brucei (ILS) Wistar Rat | Trypanosomiasis | In vivo | Unchanged parasitemia and No. of spleen Møs compared to WS-infected rats. | ↑IL-12, ↑TNF, ↑GM-CSF and ↑MIF mRNA but ↑IL-10 expression by spleen Møs from ILS-infected rats (at 4 days p.i.) compared to uninfected | MIF is highly expressed and may participate in the immune response to ILS infection, in contrast to WS infection due to a possible Møs immunosupression during WS infection. | [96] |
| T. brucei gambiense welcome strain (WS) Wistar Rat | Trypanosomiasis | In vivo | ↑Phagocytic activity, ↑IL-12, ↑TNF, ↑GM-CSF and ↑MIF mRNA but ↓IL-10 expression by spleen Møs from infected rats (4 days p.i.) compared to WS infected rats. | ↑Phagocytic activity but similar GM-CSF, M-CSF and MIF mRNA expression by ILS infected spleen Møs compared to uninfected Møs. Similar results were obtained using HS-P cells | | |

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Toxoplasmosis

Toxoplasmosis is an infectious disease caused by Toxoplasma gondii, an obligate intracellular parasite member of the phylum Apicomplexa. Immunocompromised patients are commonly affected in the brain, as well as other organs, such as the lungs, heart and eyes. Moreover, congenital toxoplasmosis is acquired if a woman contracts a primary infection while pregnant [100]. The incidence of congenital toxoplasmosis varies between countries. For example, the incidence is as high as 10 per 1,000 individuals in France [101] but only five per 10,000 in the UK [102] and one per 10,000 in the USA [103]. Interestingly, approximately one-third of the world’s population is seropositive for this parasite [104].

We found that MIF KO BALB/c mice succumbed faster to challenge with virulent (RH) and avirulent (ME49) strains of T. gondii compared to WT mice. This susceptibility was associated with a high percentage of infected peritoneal macrophages, greater numbers of cysts in brain, severe liver damage and defective early production of proinflammatory cytokines (IL-12, IL-1β, TNF-α, IL-18, IFN-γ and nitric oxide). Moreover, both WT and MIF KO mice showed comparable levels of anti-inflammatory cytokines (IL-4 and IL-10) in the sera. In contrast, we observed that the lack of MIF alters the function of CD11c+ DCs, which produce low IL-12 and TNF-α levels. Similarly, low transcript levels for IL-12, IL-1β and TNF-α were found in bone marrow dendritic cells (BMDCs) that were stimulated in vitro with STAg. Interestingly, brain tissue from patients who died of cerebral toxoplasmosis showed scarce MIF production compared to patients who died of an encephalitic cryptococcal infection. Thus, MIF appears to play a critical role in promoting resistance to toxoplasmosis by regulating the early production of innate pro-inflammatory cytokines. Additionally, lower expression of TNF-αR, IFN-γR and TLR-4 was found in PECs from infected
MIF KO mice, suggesting that the absence of MIF renders cells unable to respond rapidly to *T. gondii*. This is supported by the defective recognition of both proinflammatory cytokines and the parasite in MIF KO mice. These results are consistent with a later study in orally infected MIF KO mice [105], demonstrating that the increased mortality in *T. gondii* infected (ME49 strain) MIF KO mice is due to uncontrolled parasite replication and dissemination in brain and liver. This phenomenon was associated with low expression of MHC-II and co-stimulatory molecules (CD40, CD80 and CD86) in mononuclear lymphoid node (MLN) and splenic DCs during the early infection. In addition, low IL-12 production by MIF KO DCs was measured compared to DCs from similarly infected or STAg intravenous-injected WT mice. Moreover, MIF KO BMDCs stimulated *in vitro* with STAg or LPS showed lower expression of the parasite recognition receptor TLR11, proinflammatory cytokines (IL-12, TNF-α, IL-1β) and nitric oxide. Interestingly, these expression deficiencies were restored upon the addition of exogenous rMIF, indicating that interaction with MIF during oral *T. gondii* infection is required for DC maturation and the induction of a proinflammatory protective immune response. Additionally, a recent study has demonstrated that MIF production by chorionic villous explants from human placentas is upregulated when stimulated with STAg, particularly in the villous trophoblast. Upon release, MIF induces the dose-dependent expression of ICAM-1, primarily in the syncytiotrophoblast, leading to the adhesion of monocytes (THP-1) on the surface of villous explants. This demonstrates that MIF plays an essential role as an autocrine/paracrine mediator in *T. gondii* placental infection [51]. Related to this, de Oliveira Gomes, A., *et al.*, reported that MIF is upregulated by first-trimester placental explants and is important to control *T. gondii* infection due to a decreased parasite load at this gestational stage, in contrast to third trimester placental explants which showed increased susceptibility to infection, suggesting that variations in MIF regulation during gestation have an important role in differential susceptibility to *T. gondii* infection [106]. These findings evidence the pleiotropic role for MIF, including the maturation of important antigen presenting cells, like DCs, the expression of parasite recognition receptors, the expression of adhesion molecules, like ICAM-1, and inducing pro-inflammatory cytokines. Together, these activities are crucial for the development of a protective innate immune response to *T. gondii* infection.

**Table 4. MIF in Toxoplasmosis**

| Parasite       | Model   | Disease          | in vitro/in vivo | Treatment          | Properties                                                                 |
|----------------|---------|------------------|------------------|--------------------|---------------------------------------------------------------------------|
| *T. gondii*    | BALB/c  | Acute toxoplasmosis | *in vivo*        | Mortality compared to MIF +/+ [IL-12, IL-1β], TNF-α, IL-18 and IFN-γ in sera |
| RH strains     | MIF-KO  |                  |                  | CCR5 in PECs        | Promotes resistance inducing early production of pro-inflammatory cytokines, and TLR11 expression |
| ME49 strains   |         |                  |                  | Parasited Mø        | [121]                                                                      |
|                |         |                  |                  | Cystis in brain     |                                                                          |
|                |         |                  |                  | ALT and AST (Liver damage) |                                                                          |
|                |         |                  |                  | TNF-αR PECs         |                                                                          |
|                |         |                  |                  | IFN-γR in splenocytes |                                                                          |
|                |         |                  |                  | IL-12 and TNF-α on CD11c+ LOD DCs. |                                                                          |
| *T. gondii*    | C57BL/6 |                  | *in vitro*       | STAg or LPS         | IL-12p35, IL-12p40, IL-12p19, IL-1β and TNF-α in BMDCs                     |
| RH strain      |         |                  |                  | MIF in sera         | [106]                                                                      |
| *T. gondii*    | Human   |                  | *in vivo*        | MIF in brains from patients who died by encephalitic                  |
| *T. gondii*    | Murine  | Acute toxoplasmosis | *in vivo*        | Mortality            | Modulates the innate immunity to *T. gondii* oral infection by regulating maturation and cytokine production of DCs |
| ME49 strain    | BALB/c  |                  |                  | Brain cysts          | [105]                                                                      |
|                | MIF-KO  |                  |                  | Parasitemia and Inflammation |                                                                          |
|                |         |                  |                  | infiltrates in liver during early infection |                                                                          |
|                |         |                  |                  | MHCII, CD80, CD86 and CD40 expression in MLN DCs and splenic DCs. |                                                                          |
|                |         |                  |                  | MLN DCs producing IL-12 |                                                                          |
|                |         |                  | *in vivo*        | STAg via intravenous | IL-12 in sera                                                             |
|                |         |                  |                  | IL-12 by splenocytes. | IL-12 by splenic DCs                                                      |
Primary Amebic Meningoencephalitis

The genus *Naegleria* consists of a group of free-living amoeboflagellates (FLA) found in diverse habitats throughout the world, such as freshwater lakes, ponds, domestic water supplies, swimming pools and thermal pools [107-109]. Although over 30 species of *Naegleria* have been isolated from environmental sources, only *Naegleria fowleri* has been isolated from humans. *N. fowleri* causes primary amebic meningoencephalitis (PAM). PAM is a rapidly fatal disease affecting the central nervous system (CNS) that occurs most often in immune-competent individuals, such as children and young adults with a history of swimming and diving in freshwater [110].

Little is known about the role of MIF during amoebic parasite infection; however, a pioneer study by Cursons et al. reported that lymphocytes stimulated with *N. fowleri*, *N. jadini* and *N. gruberi* antigens released MIF, which inhibited the migration of peri-
toneal exudate cells. Moreover, guinea pigs sensitized to the three species of *Naegleria* developed typical delayed type hypersensitivity (DTH) reactions when inoculated intradermally with amoeba antigens [111]. In addition Haq, A. *et al*, showed that Peritoneal cells from hamsters sensitized with *Entamoeba histolytica* antigens (EHA) produced high MIF levels when stimulated *in vitro* with amoeba antigens, moreover the production of MIF was found to be greatly increased in animals sensitizing by EAH plus glucan [112]. MIF may be participating in the resistance to PAM and amebiasis; however, this is merely the beginning of a series of studies that aim to reveal the role of MIF, and may be helpful in the development of therapeutic treatments for this disease.

### Table 5. MIF in Amebiasis

| Parasite                        | Model     | Disease    | Treatment                              | Properties                                                                 | MIF role                                                   | Ref   |
|---------------------------------|-----------|------------|----------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------|-------|
| *Naegleria fowleri*             | Guinea pigs| PMA        | *in vivo*                               | ↑ Infiltration of mononuclear cells in lesions                              | Favors the resistance to infection (MIF is involved in the immune response against PMA) | [111] |
| *Naegleria jadinii*             | Guinea pigs| PMA        | *in vivo*                               | ↑ MIF supernatants of Lymphocytes stimulated with *Naegleria Ag*           |                                                             |       |
| *Naegleria gruberi*             | Guinea pigs| PMA        | *in vivo*                               | ↑ MIF in supernatants of Peritoneal cells from *E. histolytica*-sensitized hamsters |                                                             |       |
| *Entamoeba histolytica*         | Hamsters  | Amebiasis  | *in vivo*                               | ↑† MIF in supernatants of Peritoneal cells from *E. histolytica*-sensitized hamsters |                                                             | [112] |
|                                 | Hamsters  | Amebiasis  | *in vitro*                              | Entamoeba histolytica antigens                                             |                                                             |       |
|                                 | Hamsters  | Amebiasis  | *in vitro*                              | Entamoeba histolytica antigens + glucan                                   |                                                             |       |

Primary Amebic Meningoencephalitis (PMA)

**Neosporosis**

MIF has achieved great relevance for groups aiming to study the immune response against intracellular parasite infection. Recently, it has been studied in neosporosis [113], an infectious disease caused by *Neospora caninum*, an obligate intracellular apicomplexa parasite, closely related to *T. gondii* [114]. Neosporosis is recognized as a major cause of spontaneous abortion in cattle worldwide [114], and it has been proposed that humans are probable hosts for this parasite [115, 116].

Carvalho *et al.* found that after an *in vitro* *Neospora caninum* infection, both human uterine cervical HeLa and choriocarcinoma BeWo cells expressed high MIF levels. In this study, although BeWo cells expressed lower MIF levels than HeLa cells, BeWo cells presented a lower index of infection, decreased cell lysis, reduced parasite replication, more viability and higher TGF-β levels than HeLa cells. Additionally, pretreatment with IFN-γ reduced infected in BeWo cells, parasite replication in HeLa cells, TGF-β levels in BeWo cells and increased MIF levels in both cell types. Using IDO-specific inhibitors (1-MT), IFN-γ-mediated inhibition of parasite growth in HeLa cells was demonstated to be IDO enzyme dependent. Moreover, pretreatment with *N. caninum* lysate antigen (NLA) increased MIF levels in HeLa cells, but decreased TGF-β production in BeWo cells [113]. Given the increased MIF production by both cell types in response to IFN-γ and that *N. caninum* infection and NLA administration correlates with a low infection index and parasite replication, these results suggest that MIF may play also a role in the immune response against *N. caninum* infection in the placenta.

**Coccidiosis**

Avian coccidiosis is an intestinal infection caused by apicomplexan protozoa belonging to at least seven different species of *Eimeria* [117]. In nature, eimerian infections occur when hosts ingest sporulated oocysts, resulting in a mild or severe disease, characterized by anorexia, digestive disturbances, dehydration, blood loss, and increased susceptibility to other disease agents [118]. Coccidiosis is an important disease economically due to morbidity, mortality and reduced production efficiency of poultry and other livestock. It is estimated to be responsible for monetary losses greater than $3 billion annually [119].

Previous studies regarding the pleiotropic role of MIF have revealed its potential use as a therapeutic agent for a variety of human parasite infections; however, its role in domestic animals like poultry has only recently been investigated. Interestingly Hong *et al.*
al. found increased transcripts for MIF and other chemokines (MIP-1β, K203, IL-8 and llimphotactin), pro-inflammatory cytokines (IFN-γ, IL-1β, IL-6, IL-12, IL-15 and IL-17) and anti-inflammatory cytokines (IL-3, IL-4, IL-10, IL-13 and GM-CSF) in intraepithelial lymphocytes (IELs) from the intestinal jejunum of chickens during experimental *Eimeria maxima* infection. In addition, the authors reported high expression of the surface markers K1, CD3, CD4, CD8, TCR1 and TCR2 from different IELs subpopulations [120], which were similar to those found in experimental *Eimeria acervulina* and *Eimeria tenella* infections from an additional study [117]. Therefore, MIF, together with other chemokines, cytokines and IEL subpopulations, mediates host defense mechanisms against *Eimeria* infection. However, the role of MIF as a chemokine or a potent inducer of proinflammatory cytokines will need further clarification.

**Concluding remarks**

Since the discovery of MIF, we have witnessed slow progress in our understanding of the MIF-mediated immune mechanisms in infectious diseases, such as the protozoan parasites that cause major human diseases in the developing world, including malaria, human African trypanosomiasis, Chagas disease, leishmaniasis and toxoplasmosis. Although the life cycles of these parasites were defined years ago, specific therapeutic or preventive interventions are not yet available, and better understanding of the immune response to these protozoans is required. Recently, MIF has been considered a key player in protozoan infections, where it plays a pivotal role in early innate immunity rather than favoring the adaptive immune response. However, the role MIF plays in the response to protozoan infection is complex. For example, high levels of MIF can be dangerous for the host during malaria infections (Fig 2), on the other hand, MIF appears to be necessary to successfully control leishmaniasis, trypanosomiasis, toxoplasmosis, neoprosis, coccidiosis and meningoencephalitis (Fig 3). Together, the studies described in this review suggest that MIF participates in regulating the expression of some important molecules of the early immune response to different protozoa infections. However, the exact mechanism by which MIF acts during the immune response against parasites has not yet been defined. MIF signaling pathways have not been demonstrated for the activation of innate immunity during protozoa infections. Understanding the complex nature of these innate immunity responses will be necessary for the development of strategies to target MIF therapeutically, or for the development of a novel adjuvant or vaccine against protozoan infections.

**Figure 3.** Overview of MIF in Protozoan infections. Infected mice with intracellular protozoan (exception plasmodium) parasites (1) have high levels of MIF in serum (3) produced mainly by the immune cells (2). MIF acts in paracrine and autocrine manner (4) favoring the expression of proinflammatory cytokines and its receptors, chemokines, parasites recognition receptors and costimulatory molecules on antigen presenting cells (5). These conditions favor the microbicidal activity by macrophages, cellular chemotaxis, parasite recognition and efficient antigen presentation (6). All together indicate that MIF has a protective role against protozoan infections (7).
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Conflict of Interests

The authors have declared that no conflict of interest exists.

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