The Role of MIF in Parasitic Infections

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Abstract Macrophage migration inhibitory factor (MIF) is a pleiotropic molecule with extensive reach and numerous important roles in shaping the immune response to a large variety of infections and inflammatory diseases. MIF was first identified as a factor capable of preventing random macrophage migration in vitro in 1966 (Proc Natl Acad Sci U S A 56(1):72–77, 1966; Science 153(3731):80–82, 1966). Subsequent efforts to characterize the function of MIF have shown that the roles of this molecule extend far beyond the purview of macrophage migration and into antigen-specific responses (Cell Immunol 1:133–145, 1970) macrophage activation and survival (Proc Natl Acad Sci U S A 99(1):345–350, 2002), modulation of glucocorticoid activity to promote inflammation (Ann N Y Acad Sci 210–220, 1999; Nature 377(6544):68–71, 1995), T cell activation (Proc Natl Acad Sci U S A 93(15):7849–7854, 1996), and macrophage phagocytosis (Immunology 92(1):131–137, 1997). MIF also is involved in the coordination between the innate and adaptive immune response. Due to the sheer number of functions performed by MIF during the immune response, its role during parasitic infections has come under increased scrutiny. Interestingly, MIF has been found to be a critical mediator of immunity against a broad range of parasite infections. Here we summarize the findings relevant to the role of MIF during parasitic infections.

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1 The Role of MIF in Malaria

Malaria is a vector-borne parasitic disease which is spread by the bite of female mosquitoes and is caused by organisms of the genus *Plasmodium*. According to the WHO, there were just under 165 million cases of malaria in 2013, with an estimated 854,000 deaths, making malaria one of the most severe infectious diseases in the world. The vast majority of malaria-related deaths were children under the age of 5 [1]. *Plasmodium* infects hepatocytes and erythrocytes in humans and by infecting these cells survives and avoids excessive exposure to the immune system [2–4].

Innate immunity to *Plasmodium* is minimal at best, and acquired immunity is often only observed in those with repeated exposure to the parasite [5, 6]. Complete resistance to malaria infection is often associated with genetic factors, as genes for sickle cell anemia as well as thalassemia and glucose-6-phosphate dehydrogenase deficiency are commonly associated with resistance [7]. Due to the lack of effective human resistance and the hemolytic nature of the disease, the parasite is often able to spread systemically and cause complications including cerebral malaria (CM) and severe anemia, especially in children who have not developed resistance through repeated exposure [8].

Experimental models of malaria have emphasized that the early immune response to *Plasmodium* has the potential to change the course of the disease and prevent or promote complications such as CM and anemia. Numerous studies have suggested a protective role against blood-stage *Plasmodium* parasites for pro-inflammatory, Th1-associated molecules in blood serum such as IL-12 [9], IFN-γ [10–12], and TNF-α [13]. These pro-inflammatory cytokines are primarily responsible for the induction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by macrophages and monocytes, which play an active role in the elimination of blood-stage parasites during erythrocyte phagocytosis in the spleen [11, 13]. While there is a large amount of evidence to suggest a protective role for the generation of Th1-type inflammation, numerous studies have paradoxically implicated higher serum concentrations of IFN-γ, IL-12, and TNF-α with enhanced pathology [6]. One study links high serum concentrations of the anti-inflammatory molecule IL-10 with protection from CM and anemia [14]. Indeed, some studies have indicated that mortality in children may not be due to a lack of exposure [15] and could be instead due to a systemic overproduction of inflammatory factors such as IFN-γ during reinfection [16, 17]. Thus elimination of *Plasmodium* requires a delicate balance in the immune response to avoid damage to the host and efficiently eliminate the parasite.

One of the factors which underlie this balance is macrophage migration inhibitory factor (MIF). MIF has been shown to function directly in promoting activation and survival of innate immune cells [18–21] and has also been demonstrated to promote activation of T cells [22]. MIF's activity has come under increased scrutiny due to research suggesting that protective immune responses to *Plasmodium* may be dependent on the early immune response by circulating lymphocytes [23]. Importantly, MIF has been shown to be essential in promoting systemic inflammation during the septic shock response [24, 25], underlining its potential importance

during blood-stage *Plasmodium* infections. Numerous studies have shown the importance of MIF during malaria. One study of severe malaria in children associated pathology with a decrease in circulating MIF and MIF transcripts and noted that enhanced MIF expression correlated with high concentrations of IFN-γ and IL-12 in plasma [26]. A separate study of Indian malaria patients noted that genetic abnormalities in the MIF-encoding region and subsequent decreases in MIF expression were correlated with susceptibility [27]. This finding was corroborated by a second genetic study in Kenyan children which focused on mutations in the promoter of the MIF genetic locus, with a noted increase in rates of severe parasitemia among those with mutations in the MIF promoter [28]. Additionally, a study of children with histories of mild or severe malaria found that cases of mild malaria were associated with higher overall concentrations of MIF and MIF transcripts in blood [29, 30]. These studies have outlined a potentially critical role for host-derived MIF expression in limiting complications during malaria.

Interestingly, one study of circulating lymphocyte populations during experimental infections with *P. falciparum* showed that MIF concentrations in sera were reduced precipitously along with concentrations of circulating lymphocytes at the start of the blood-stage of parasitic infection [31]. This raises the possibility that the parasite could downregulate concentrations of host-derived MIF during the start of its symptomatic phase, when it is exposed to circulating monocytes and lymphocytes and therefore vulnerable to immune attack.

As is the case with other pro-inflammatory molecules, MIF expression has also been correlated with the appearance of severe symptoms such as CM and anemia. A study of Indian cerebral malaria patients indicated that higher serum concentrations of MIF in peripheral blood were associated with mortality [32]. Interestingly, in experimental models of malarial anemia, MIF also had an important role. In this model, MIF expression was enhanced by macrophages after hemozoin (malarial pigment) uptake and was correlated with inhibition of erythropoiesis during malaria. This study concluded that MIF expression likely contributed to the observed anemia in malaria patients by inhibition of erythropoiesis [33]. A separate study showed that mice genetically deficient in MIF were more resistant to malarial anemia and displayed a decreased mortality rate in comparison with wild-type controls [34]. However a study in humans showed that MIF levels decreased, while anemia severity augmented during the course of the infection. Diminished levels of MIF were associated with reduced MIF production by monocytes after hemozoin uptake [29, 30]. Thus MIF may play a fundamental role in anemia caused by malaria and also a detrimental inflammatory role during cerebral malaria.

Interestingly *Plasmodium*, like several of the other parasites discussed in this chapter, express a MIF orthologue [35, 36] which is often referred to as *Plasmodium* MIF or PMIF. The expression of this orthologue has become a major topic among malaria researchers because of its potential to modulate the immune response through mimicry or nullification of MIF activity [37]. Recent work with murine infections with *P. yoelii* genetically deficient in MIF has revealed that these MIF orthologues may play a major role in regulation of the parasite's growth, particularly during the liver stage of infection. This study noted that PMIF−/− parasites

were viable and replicated normally in the mosquito vector but also found that the parasite's infection of hepatocytes and subsequent establishment of infection were interrupted [38]. Murine infections with transgenic *P. yoelii* which overexpressed PMIF supported these findings and showed that the parasites were able to establish liver-stage murine infections but developed lower parasitemias with decreased mortality [39].

The mechanisms by which PMIF might modulate the immune response during *P. yoelii* infection were recently investigated using recombinant PMIF. One study by Zhang et al. noted that in vitro incubation with recombinant PMIF inhibited random migration of $CD11b^+$ cells, as is MIF's canonical function, but noted that the release of IL-12, IL-10, TNF-α, and IL-6 by these cells was neither elicited by PMIF incubation nor modulated by PMIF when it was incubated alongside LPS. Additionally, this study reported that the recruitment of inflammatory monocytes from the spleen was altered when PMIF was administered prior to *P. yoelii* infection and noted that populations of activated inflammatory monocytes in both the spleen and serum of infected mice were greatly enhanced by immunization against PMIF [39]. A study by Shao et al. determined that PMIF, like mammalian MIF, elicits a chemotactic response by monocytes in vitro [40]. Another study by Cordery et al. determined that treatment of monocytes with PMIF from *P. falciparum* decreased membrane expression of TLR2 and TLR4, as well as the costimulatory molecule CD86. Additionally, monocyte migration was inhibited in PMIF-treated monocytes. Importantly, this study also noted that PMIF itself was not sufficient to elicit cytokine release from monocytes, which matched the trends observed by Zhang et al. [35, 39]. Localization of PMIF showed that PMIF was excreted from *P. falciparum* during its intraerythrotic stage and accumulated in red blood cells prior to hemolysis. This finding points to an immunomodulatory role for the PMIF which is released when the erythrocyte bursts and the parasite once again comes into contact with the host immune system [35].

In human infections, the study by Cordery et al. showed that PMIF elicits an antibody response but noted that the serum concentration of PMIF antibodies did not correlate with the stage of the disease. The antibody titers of patients followed over the course of this study fell significantly after the resolution of the infection, which suggests that humoral immunity to PMIF may be transient at best [35]. However, a study by Han et al. showed that higher concentrations of PMIF were associated with increased disease severity in human infections with *P. falciparum* and *P. vivax* [41].

While the role of MIF in *Plasmodium* infections is complex and further complicated by the presence of both human and *Plasmodium* orthologues, the research surrounding MIF has indicated that its role is quite extensive. The exact mechanisms of MIF and PMIF activity have yet to be fully elucidated, but early work has shown that MIF's role in counteracting glucocorticoid suppression may be crucial to the development of a balanced immune response to *Plasmodium* parasites. The numerous roles and responsibilities which have been attributed to MIF have ensured that it will be a major topic of investigation by malaria researchers for years to come.

2 The Role of MIF in Toxoplasmosis

Toxoplasma gondii is an intracellular protozoan parasite which infects most warm-blooded animals, including humans, and is the causative agent of the disease toxoplasmosis. Cats and other felines serve as the definitive host in which the sexual cycle of the parasite takes place. In humans, the parasites invade a broad range of tissues, including the brain and muscles, and are usually found forming cysts [42, 43]. It is estimated that almost one third of the human population is infected with *Toxoplasma* [44]. Disease transmission is accomplished by several means, including the consumption of undercooked or contaminated meat, consumption of contaminated water, and exposure to contaminated cat feces, and also by congenital transmission [43, 45].

Most *Toxoplasma* infections in humans are asymptomatic, owing largely to the parasite's intracellular lifestyle and its adaptation to life inside of the human host. Symptomatic infections occur in approximately 10–20% of patients, with common clinical manifestations including lymphadenopathy, fever, headaches, and generalized myalgias [42]. Immunocompromised patients, as well as pregnant women and newborns, are at increased risk of severe complications. In severe cases, toxoplasmosis can disseminate to other areas of the body and damage the brain, heart, skeletal muscle, and intestines [44].

Once the parasite has infected the host, *T. gondii* is able to infect phagocytic cells and nonprofessional phagocytes [46]. The parasite infects the cell in an active invasion process which mediates the formation of the parasitophorous vacuole which is related with successful infection. Also, phagocytosis of the parasite is a common route of infection for professional phagocytes [47, 48].

The immune response which confers protection against toxoplasmosis is largely associated with an optimal CD4+ and CD8+ T cell response. The innate-derived cytokine IL-12 is a major player in resistance against toxoplasmosis. This cytokine is mainly released by dendritic cells and plays a fundamental role inducing IFN-γ by natural killer (NK) cells and CD4+ and CD8+ T cells [49]. IFN-γ promotes host protection via multiple mechanisms including induction of immunity-related GTPases (IRGs) and guanylate-binding proteins (GBPs). The release of IFN-γ also triggers the induction of nitric oxide and reactive oxygen species and is responsible for changes in host metabolism that restrict *T. gondii* replication [50].

Factors which modulate inflammation are critical to the clearance of *Toxoplasma* from the host. MIF, as a potent regulator of the inflammatory response, has been shown to be important in resistance against this parasite. Animal studies conducted using both BALB/c and C57BL/6 mice genetically deficient in MIF have shown a possible protective role for MIF during *T. gondii* infection. MIF−/− mice from both genetic backgrounds were more susceptible to intraperitoneal infection with both the highly virulent RH and the moderately virulent ME49 strains of *T. gondii*. Additionally, it was noted that MIF-deficient mice develop significantly greater liver and brain pathology than wild-type controls [51]. Another study using orally infected BALB/c MIF−/− mice showed similar results, demonstrating that MIF is

essential to resistance in both intraperitoneal and oral parasitic inoculations. Interestingly in MIF-deficient mice, dendritic cells from mesenteric lymph node displayed a less mature phenotype (decreased MHCII, CD80, and CD86 expression) and low IL-12 production compared with WT DCs. In vitro complementary studies by this group showed that bone marrow-derived dendritic cells lacking MIF had an impaired response to *Toxoplasma*-soluble antigens in vitro, strongly suggesting that autocrine MIF production is required for an efficient response of DCs to this pathogen since exogenous MIF restored MIF−/− DC function [52]. In agreement with these findings, oral infection with *T. gondii* in C57BL/6 MIF−/− mice resulted in increased parasitic loads in the intestine accompanied with reduced intestinal inflammation. Of note, oral infection with *T. gondii* in C57BL/6 mice causes inflammatory bowel disease, and the mice died after 15 days of infection, contrary to BALB/c mice which survive [53]. Surprisingly the absence of MIF in C57BL/6 mice also resulted in increased survival compared with MIF-sufficient mice, which died early and showed intestinal inflammation and pathology [54]. This indicates that in this genetic background, MIF can be deleterious for the host, promoting exacerbated inflammation. Interestingly, patients who died from cerebral toxoplasmosis showed little MIF expression in the brain [51].

Because of the potential for severe complications in pregnant women and fetuses, there is significant interest in understanding the immune response to *T. gondii* during pregnancy. Studies have shown an important role for MIF in controlling *Toxoplasma* in placental explants. In vitro infections of human placental explants from the first trimester displayed increased concentrations of MIF and a reduction in the total number of *Toxoplasma* parasites. Explants from the third trimester were more susceptible than those from the first trimester and did not produce MIF. Addition of exogenous MIF was sufficient to decrease parasite loads in both first and third trimester explants [55]. It has also been observed that MIF acts on trophoblasts to control *T. gondii* infection in vitro. Addition of exogenous MIF to infected trophoblasts resulted in reduced parasitic loads when MIF was added at higher concentrations [56].

Overall, the experimental data suggest that MIF is an important mediator of protection during toxoplasmosis. MIF could act enhancing microbicidal mechanisms of macrophages and also increasing their response to cytokines related with protection, for example, by overexpression of TNF-αR and IFN-γR [53]. Together these studies shown that MIF is an important molecule mediating resistance against *Toxoplasma gondii* infection.

3 The Role of MIF During Trypanosomiasis

Trypanosomiasis is a vector-borne disease caused by protozoan parasites of the genus *Trypanosoma*. *Trypanosoma cruzi* is the causative agent of Chagas disease in the Americas, and *Trypanosoma brucei* causes African sleeping sickness. *T. cruzi* transmission occurs when infected triatomine feces contaminate a bite site or mucous membranes. Entering trypomastigotes invade macrophages and differentiate into the

replicative amastigote form before disseminating into the heart, skeletal muscles, and brain. *T. brucei* is transmitted by the bite of an infected tsetse fly. Following the bite, trypomastigotes enter the bloodstream where they replicate extracellularly.

Resistance to *T. cruzi* is dependent on the activation of the innate and adaptive immune responses as mediated by NK cells and macrophages and CD4+ T cells, CD8+ T cells, and B cells, respectively [57, 58]. Pro-inflammatory cytokines that regulate NK cell and macrophage activity like IFN-y, IL-12, and TNF-α play an important role in disease resolution, as does NO production [59–61].

Several groups have examined the role of MIF during trypanosomiasis. Using genetically MIF-deficient mice, Reyes et al. found that MIF−/− BALB/c mice infected with *T. cruzi* displayed increased mortality and higher levels of parasitemia in skeletal muscle and cardiac tissue. Serum from MIF−/− infected mice showed reduced production of the pro-inflammatory cytokines IL-12, TNF-α, IFN-y, IL-1β, and IL-18, with the most pronounced differences at early time points of the infection. Despite severe pathology, hearts from MIF−/− mice had lower mRNA expression of iNOS, IL-12 p35, IL-12 40, and IL-23, suggesting that decreased production of pro-inflammatory cytokines may be responsible for susceptibility. A deficiency in Th1 polarization was reflected by decreased titers of IFN-γ-associated IgG2a [62]. Interestingly, serum levels of the anti-inflammatory cytokines IL-10 and IL-4 were not elevated in MIF−/− mice, eliminating the possibility that a switch of a protective Th1 to Th2 permissive response was the cause of the observed increase in mortality. These data suggest that MIF is necessary for the upregulation of pro-inflammatory cytokines and the generation of a Th1 response during experimental Chagas disease.

Terrazas et al. corroborated the finding that MIF−/− BALB/c mice infected with *T. cruzi* develop increased parasitemia and mortality. In this study, the authors evaluated the early response against *T. cruzi*. Interestingly, MIF levels in serum were increased as early as 12 h post-infection and gradually rose during the first 3 days of infection. In line with early production of MIF during *T. cruzi* infection, other pro-inflammatory cytokines such as IL-1β, IL-12, TNF-α, and IFN-γ were induced early during the infection; however the serum levels of all these cytokines were significantly reduced in MIF-deficient mice.

As a possible cause of the initial impaired inflammatory response in MIF-deficient mice, they found that MIF had an important role during DC activation in vivo and found that DCs had reduced expression of MHC-II, CD80, CD86, OX40L, and IL-12 in the absence of MIF. The authors confirmed these findings in MIF−/− bone marrow-derived DCs in vitro, showing that MIF-deficient DCs had the same reduction in costimulatory molecules as well as impaired IL-12 and TNF-α production in response to *T. cruzi* antigen. Interestingly, addition of exogenous MIF to MIF−/− DCs restored the ability of these cells to efficiently respond to *T. cruzi* antigens in a p38 MAPK-dependent pathway. The inability of MIF-deficient DCs to fully mature and produce IL-12 could help to explain the impaired Th1-associated response observed in mice [63]. However, it is still unknown whether MIF regulates the accumulation or trafficking of DCs or their precursors in vivo or whether MIF affects the activation of a particular subset of DCs.

A study looking at expression profiles in cardiac and skeletal muscle tissue of *T. cruzi*-infected BALB/c mice found high levels of MIF mRNA at early and late

time points. In agreement with the study conducted by Terrazas et al., high MIF expression was observed prior to the induction of TNF-α, IFN-y, or iNOS, suggesting that MIF is part of the primary immune response to *T. cruzi* and is upstream to the expression of pro-inflammatory genes. Histological analysis identified infiltrating lymphocytes as major producers of MIF [64]. Further study is needed to elucidate the role of MIF in different immune cell populations.

Fewer studies have examined the role of MIF in *T. brucei* infection. During *T. brucei* infection, a strong Th1 immune response is required for initial parasite control; however, a persistent pro-inflammatory immune response during the chronic stage is associated with tissue damage, anemia, and increased pathogenicity [65–67]. During the acute phase of *T. brucei* infection in C57BL/6 mice and rats, MIF has been found to be upregulated along with pro-inflammatory genes [68].

A single study by Stijlemans et al. examined the role of MIF in chronic *T. brucei* infection. Similar to *T. cruzi* infection, C57BL/6 MIF−/− mice infected with *T. brucei* had lower serum concentrations of pro-inflammatory IFN-γ and TNF-α at all time points. MIF−/− mice lived an average of 10 days longer than WT mice before succumbing to infection, although no difference was observed in the degree of parasitemia. The same results were achieved using anti-MIF IgG treatment. During the chronic stage of infection, MIF−/− mice had higher serum IL-10 production, reduced liver pathology, and reduced infiltration of inflammatory monocytes and neutrophils into the liver. The altered cell populations were likely due to the reduced expression of the chemokines CCL2, CXCL1, and CXCL5 [69]. It is worth noting that another study looking at the acute stage of *T. brucei* infection showed no reduction of monocyte egress in MIF-deficient mice at 6 days post-infection [70]. Stijlemans et al. isolated neutrophils and monocytes from WT mice with chronic *T. brucei* infection and adoptively transferred them into infected MIF−/− mice (24 dpi). Adoptive transfer of WT neutrophils, but not inflammatory monocytes, into MIF−/− mice increased MIF concentrations and restored MPO activity and TNF-α production. Transfer of WT neutrophils also increased ALT and AST levels in the sera, indicating increased hepatocyte damage. These data suggest that the mechanism for liver injury is MIF dependent for neutrophils, but not for inflammatory monocytes. Additionally, MIF−/− mice had reduced red blood cell death, increased iron bioavailability, and more robust erythropoiesis during later time points of infection. Overall, this study showed a modestly detrimental role of MIF during the chronic stage of *T. brucei* infection [69]. These studies demonstrate an important role for MIF to control *T. cruzi* infection however also indicate that MIF production can result in pathology during *T. brucei* infection.

4 The Role of MIF in Leishmaniasis

Leishmania is a protozoan parasite transmitted by the bite of the sand fly of the genus *Phlebotomus* and *Lutzomyia*. *Leishmania* promastigotes are subdermally inoculated into the host by infected sand flies and are rapidly phagocytosed by

recruited neutrophils. Infected neutrophils then die by apoptosis and are phagocytosed by macrophages or dendritic cells [71]. Once inside the macrophage, the parasite undergoes a morphological switch to its amastigote form, which replicates inside of the phagocyte and causes ulcers in the skin (cutaneous leishmaniasis) or spreads to the bone marrow, spleen, and liver (visceral leishmaniasis) depending of the *Leishmania* species. It is well accepted that the elimination of the parasite relies on the ability of the macrophage to produce nitric oxide. However, the levels of nitric oxide are usually low when the macrophages are infected with *Leishmania* in vitro. The elimination of the parasite requires further stimulation of the infected macrophage with IFN-γ, which triggers nitric oxide production and subsequent elimination of the parasite [72–74]. Studies in experimental models of leishmaniasis have indicated the importance of MIF in parasite elimination. In vitro experiments first demonstrated that stimulation of macrophages with recombinant MIF enhanced parasite killing of *Leishmania major.* The leishmanicidal activity of MIF was dependent on enhanced TNF-α and nitric oxide production [75]. In agreement with this report, MIF-deficient mice were susceptible to *L. major* infection, displaying larger lesions and higher parasite numbers than control mice. Interestingly, the absence of MIF did not affect IFN-γ and IL-4 production during the course of the disease. However, MIF-deficient macrophages displayed reduced nitric oxide and superoxide production in response to IFN-γ compared to MIF-sufficient macrophages. These defects were reflected in the impaired ability of MIF−/− macrophages to eliminate *L. major* in vitro [76]. Thus, in this model, MIF did not affect the Th1 or Th2 response but rather affected macrophage function. Importantly, MIF-producing CD4+ T cells were shown to play an important role mediating protection against *Leishmania pifanoi* after experimental vaccination [77]. The presence of MIF during leishmaniasis has been corroborated in humans. In one study on patients with cutaneous leishmaniasis, MIF levels in serum were elevated [78]. Also, patients with active visceral leishmaniasis caused by *Leishmania infantum* had elevated levels of MIF in serum; however, those patients in remission showed decreased levels of MIF in circulation [79]. As with other parasites, *Leishmanias* also express MIF orthologues. *L. major* secretes two isoforms of MIF that bind to CD74 on macrophages and induce ERK1/ERK2 activation. This pathway reduces apoptosis of infected macrophages and extends parasite survival [80]. Together, these studies show an important role of MIF during leishmaniasis where MIF not only acts by promoting accumulation of macrophages but also has an active role inducing parasite killing.

5 The Role of MIF in Helminth Infections

Helminthes are macroparasites which commonly cause nonlethal disease. However, they usually establish chronic infections in their host. They invade a broad range of organs including the intestine, lungs, liver, lymph nodes, and brain. Despite significant helminth diversity, the immune response mounted against helminth parasites is

most frequently a polarized Th2 response, with elevated production of IL-4, IL-5, and IL-13. These parasites also enhance the production of the regulatory cytokine IL-10. The accumulation of eosinophils and the polarization of macrophages toward an alternatively activated state is also hallmark of helminth infections [81]. Despite the importance of MIF in different infections, there are few reports about how MIF participates in immunity against these macroparasites.

MIF was first reported to be produced in response to experimental schistosomiasis by splenocytes after 8 weeks of infection; however MIF levels were not sustained and decreased over the time [82]. The importance of MIF during schistosomiasis was tested later, where administration of blocking antibodies against MIF resulted in elevated numbers of adult worms but decreased ova production. This effect was seen only when MIF was blocked after 4–6 weeks post-infection [83]. The importance of MIF has been also investigated during cestode infection. During experimental cysticercosis with the metacestode *Taenia crassiceps*, MIF-deficient mice displayed enhanced susceptibility, presenting increased parasitic burdens after 8 weeks post-infection. Interestingly, MIF−/− mice produced similar levels of IL-4 and IFN-γ than their WT counterparts. The susceptibility of MIF-deficient mice against this helminth was associated with the inability of MIF−/− macrophages to produce inflammatory cytokines and nitric oxide [84]. A well-known mechanism of defense against pathogens is the formation of the granuloma, which is commonly structurated with macrophages at its core and surrounded with a variety of immune cells. This structure restricts the spreading or migration of the invading organisms. Interestingly, the granulomas formed in the liver of *S. japonicium*- and in the brain of *T. crassiceps*-infected mice showed enhanced MIF expression [85]. As of yet, it is not known whether MIF deficiency affects granuloma formation or function during helminth infections and has to be further investigated. Apart of the mammalian host, MIF is also important for protection against helminth infection in other organisms. Recently, MIF was detected in snails, a host for schistosomas. Of note, circulating hemocytes expressed MIF, and knockdown of MIF expression in the snail resulted in increased parasite burdens [86], indicating the preserved evolutionary function of MIF as an important molecule for immune function.

Similar to protozoan parasites, helminth parasites express MIF orthologues. Helminth parasite-derived MIF has been shown to interact with the immune system and exert immunomodulatory functions. The filarial parasite *Brugia malayi* secretes MIF, which has 40% homology to human MIF. Similar to human MIF, filarial MIF has the ability to inhibit macrophage migration and also function as a monocyte/macrophage chemoattractant [87]. In addition, *B. malayi* MIF was able to upregulate *Ym1* expression, an alternatively activated macrophage-associated gene, and enhance the recruitment of eosinophils in vivo [88]. Filarial MIF also upregulated the expression of IL-4 receptor on macrophages, thus enhancing their response to IL-4 [89].

In line with the anti-inflammatory properties of helminth-derived MIF, the administration of secreted MIF from *Anisakis simplex* had a beneficial effect in a model of allergic airway inflammation and colitis by augmenting IL-10 production in mice [90, 91]. Also, *Anisakis*-derived MIF downregulated the production of Th2

cytokines in an in vitro culture of peripheral blood mononuclear cells from asthmatic patients [92]. Interestingly, host-derived MIF plays a detrimental role during inflammation, by exacerbating the immune response [93]. In this context, it is possible that parasite-derived MIF competes for the receptors of mammalian MIF, blocking its inflammatory activity. This could be a strategy for the parasite to dampen the host immune response and survive. An evidence of this thought is that a DNA-based vaccine expressing *Trichinella spiralis* MIF promoted a Th1 response and conferred partial protection against *T. spiralis* infection [94], strongly suggesting that parasite-derived MIF could be one of the multiple mechanisms of immune evasion used by helminths. Interestingly, there are no data regarding the role of MIF during helminth intestinal infection, which represents the more common manifestation associated with these organisms. Together these findings identify MIF as an important molecule in the immune response against helminth parasites.

6 Final Remarks

Macrophage migration inhibitory factor (MIF) which is expressed by a variety of immune cells such as monocytes, macrophages, dendritic cells, B cells, T cells, neutrophils, eosinophils, mast cells and basophils was discovered in 1966 and studied as a mediator of delayed type hypersensitivity reactions [95–99]. Here we have presented evidence of the key role of MIF during parasitic infections. In most scenarios, MIF is important to efficiently eliminate parasitic infections, mainly by promoting an efficient response by macrophages and dendritic cells. However, during malaria or *T. brucei* infection, MIF production appears to have an especially complex role, enhancing the inflammatory response and promoting tissue damage. The source of MIF during parasitic infections is still a matter of investigation, but the available evidence points to an early innate immune cell population which initially encounters the pathogen, triggering the release of MIF and promoting an appropriate expression of pattern recognition receptors and the subsequent activation of the cytokine response. Finally, detailed mechanisms of how MIF helps to restrain parasite infections remain to be investigated.

References

1. Murray CJL et al (2014) Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden Of Disease Study 2013. Lancet 384(9947):1005–1070. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=4202387&Tool=Pmcentrez&Rendertype=Abstract
2. Baer K et al (2007) Release of hepatic Plasmodium yoelii merozoites into the pulmonary microvasculature. PLoS Pathog 3(11):1651–1668
3. Frevert U et al (2005) Intravital observation of Plasmodium berghei sporozoite infection of the liver. PLoS Biol 3(6):1034–1046

4. Vaughan AM, Aly ASI, Kappe SHI (2008) Malaria parasite pre-erythrocytic stage infection: gliding and hiding. Cell Host Microbe 4:209–218
5. Baird JK et al (1998) Age-dependent susceptibility to severe disease with primary exposure to Plasmodium falciparum. J Infect Dis 178:592–595
6. Mshana RN et al (1991) Cytokines in the pathogenesis of malaria: levels of IL-I beta, IL-4, IL-6, TNF-alpha and IFN-gamma in plasma of healthy individuals and malaria patients in a holoendemic area. J Clin Lab Immunol 34:131–139. Http://Ovidsp.Ovid.Com/Ovidweb.Cgi?T=Js&Csc=Y&News=N&Page=Fulltext&D=Med3&An=1667945; Http://Digitaal.Uba.Uva.Nl:9003/Uva-Linker?Sid=Ovid:Medline&Id=Pmid:1667945&Id=Doi:&Issn=0141-2760&Isbn=&Volume=34&Issue=3&Spage=131&Pages=131-9&Date=1991&Title=Journal+O
7. López C et al (2010) Mechanisms of genetically-based resistance to malaria. Gene 467(1–2):1–12. Http://Dx.Doi.Org/10.1016/J.Gene2010.07.008
8. Griffin JT et al (2015) Gradual acquisition of immunity to severe malaria with increasing exposure. Proc R Soc B Biol Sci 282:20142657. Http://Rspb.Royalsocietypublishing.Org/Content/282/1801/20142657
9. Bastos KRB et al (2002) Impaired macrophage responses may contribute to exacerbation of blood-stage Plasmodium chabaudi chabaudi malaria in interleukin-12-deficient mice. J Interferon Cytokine Res 22(12):1191–1199. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/12581492
10. Franklin BS et al (2009) Malaria primes the innate immune response due to interferon-gamma induced enhancement of toll-like receptor expression and function. Proc Natl Acad Sci U S A 106(14):5789–5794. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2657593&Tool=Pmcentrez&Rendertype=Abstract
11. Shear HL et al (1989) Role of IFN-gamma in lethal and nonlethal malaria in susceptible and resistant murine hosts. J Immunol 143(6):2038–2044
12. Su Z, Stevenson MM (2000) Central role of endogenous gamma interferon in protective immunity against blood-stage plasmodium chabaudi as infection. Infect Immun 68(8):4399–4406. Http://Iai.Asm.Org/Content/68/8/4399\N; http://Iai.Asm.Org/Content/68/8/4399.Full.Pdf\N; http://Iai.Asm.Org/Content/68/8/4399.Short
13. Jacobs P, Radzioch D, Stevenson MM (1996) A Th1-associated increase in tumor necrosis factor alpha expression in the spleen correlates with resistance to blood-stage malaria in mice. Infect Immun 64:535–541
14. Kurtzhals JA et al (1998) Low plasma concentrations of interleukin-10 in severe malarial anaemia compared with cerebral and uncomplicated malaria. Lancet 351:1768–1772
15. Erunkulu OA et al (1992) Severe malaria in Gambian children is not due to lack of previous exposure to malaria. Clin Exp Immunol 89(2):296–300. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=1554452&Tool=Pmcentrez&Rendertype=Abstract
16. Artavanis-Tsakonas K, Tongren JE, Riley EM (2003) The war between the malaria parasite and the immune system: immunity, immunoregulation and immunopathology. Clin Exp Immunol 133(2):145–152
17. Riley EM et al (1991) Immune-response to soluble exoantigens of Plasmodium falciparum may contribute to both pathogenesis and protection in clinical malaria—evidence from a longitudinal, prospective-study of semi-immune African children. Eur J Immunol 21(4):1019–1025. <Go To Isi>://A1991fj28400023
18. Calandra T et al (1994) The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. J Exp Med 179(6):1895–1902
19. Mitchell RA et al (2002) Macrophage migration inhibitory factor (MIF) sustains macrophage proinflammatory function by inhibiting P53: regulatory role in the innate immune response. Proc Natl Acad Sci U S A 99(1):345–350
20. Murakami H et al (2002) Macrophage migration inhibitory factor activates antigen-presenting dendritic cells and induces inflammatory cytokines in ulcerative colitis. Clin Exp Immunol 128(3):504–510. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=1906246&Tool=Pmcentrez&Rendertype=Abstract

21. Onodera S et al (1997) Macrophage migration inhibitory factor induces phagocytosis of foreign particles by macrophages in autocrine and paracrine fashion. Immunology 92(1):131–137
22. Bacher M et al (1996) An essential regulatory role for macrophage migration inhibitory factor in T-cell activation. Proc Natl Acad Sci U S A 93(15):7849–7854
23. Scragg IG et al (1999) Early cytokine induction by Plasmodium falciparum is not a classical endotoxin-like process. Eur J Immunol 29:2636–2644
24. Bernhagen J et al (1993) MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. Nature 365(6448):756–759
25. Bozza M et al (1999) Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis. J Exp Med 189(2):341–346
26. Awandare GA et al (2006) Decreased circulating macrophage migration inhibitory factor (MIF) protein and blood mononuclear cell MIF transcripts in children with Plasmodium falciparum malaria. Clin Immunol 119(2):219–225. Http://Www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=16461006\N; http://Www.Sciencedirect.Com/Science?_Ob=Mimg&_Imagekey=B6wcj-4j6wp83-1-5&_Cdi=6740&_User=1535037&_Orig=Search&_Coverdate=05/31/2006&_Sk=998809997&View=
27. Jha AN et al (2013) Variations in ncRNA gene LOC284889 and MIF-794CATT repeats are associated with malaria susceptibility in indian populations. Malar J 12(1):345. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3849407&Tool=Pmcentrez&Rendertype=Abstract
28. Awandare GA et al (2009) MIF (macrophage migration inhibitory factor) promoter polymorphisms and susceptibility to severe malarial anemia. J Infect Dis 200(4):629–637. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3607439&Tool=Pmcentrez&Rendertype=Abstract
29. Awandare GA et al (2007a) Higher production of peripheral blood macrophage migration inhibitory factor in healthy children with a history of mild malaria relative to children with a history of severe malaria. Am J Trop Med Hyg 76(6):1033–1036. Http://Www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=17556607
30. Awandare GA et al (2007b) Role of monocyte-acquired hemozoin in suppression of macrophage migration inhibitory factor in children with severe malarial anemia. Infect Immun 75(1):201–210
31. De Mast Q et al (2008) A decrease of plasma macrophage migration inhibitory factor concentration is associated with lower numbers of circulating lymphocytes in experimental Plasmodium falciparum malaria. Parasite Immunol 30(3):133–138. Http://Www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=18179626
32. Jain V et al (2009) Macrophage migration inhibitory factor is associated with mortality in cerebral malaria patients in India. BMC Res Notes 2:36. Http://Www.Ncbi.Nlm.Nih.Gov/Entrez/Query.Fcgi?Cmd=Retrieve&Db=Pubmed&Dopt=Citation&List_Uids=19284533\N; http://Www.Biomedcentral.Com/Content/Pdf/1756-0500-2-36.Pdf
33. Martiney JA et al (2000) Macrophage migration inhibitory factor release by macrophages after ingestion of plasmodium chabaudi-infected erythrocytes: possible role in the pathogenesis of malarial anemia. Infect Immun 68(4):2259–2267. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=97412&Tool=Pmcentrez&Rendertype=Abstract
34. Mcdevitt MA et al (2006) A critical role for the host mediator macrophage migration inhibitory factor in the pathogenesis of malarial anemia. J Exp Med 203(5):1185–1196. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2121202&Tool=Pmcentrez&Rendertype=Abstract
35. Cordery DV et al (2007) Characterization of a Plasmodium falciparum macrophage-migration inhibitory factor homologue. J Infect Dis 195(6):905–912. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/17299722
36. Dobson SE et al (2009) The crystal structures of macrophage migration inhibitory factor from Plasmodium falciparum and Plasmodium berghei. Protein Sci 18(12):2578–2591. <Go To Isi>://000272757200015

37. Augustijn KD et al (2007) Functional characterization of the Plasmodium falciparum and P. berghei homologues of macrophage migration inhibitory factor. Infect Immun 75(3):1116–1128
38. Miller JL et al (2012) Plasmodium yoelii macrophage migration inhibitory factor is necessary for efficient liver-stage development. Infect Immun 80:1399–1407
39. Zhang Y et al (2012) Macrophage migration inhibitory factor homolog from Plasmodium yoelii modulates monocyte recruitment and activation in spleen during infection. Parasitol Res 110(5):1755–1763. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/22015474
40. Shao D et al (2008) Detection of Plasmodium falciparum derived macrophage migration inhibitory factor homologue in the sera of malaria patients. Acta Trop 106(1):9–15. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/18262164
41. Han C et al (2010) Plasma concentration of malaria parasite-derived macrophage migration inhibitory factor in uncomplicated malaria patients correlates with parasitemia and disease severity. Clin Vaccine Immunol 17(10):1524–1532
42. Dubey JP (1998) Advances in the life cycle of Toxoplasma gondii. Int J Parasitol 28(7):1019–1024
43. Robert-Gangneux F, Dardé M-L (2012) Epidemiology of and diagnostic strategies for toxoplasmosis. Clin Microbiol Rev 25(2):264–296. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3346298&Tool=Pmcentrez&Rendertype=Abstract
44. Montoya JG, Liesenfeld O (2004) Toxoplasmosis. Lancet 363(9425):1965–1976
45. Hill D, Dubey JP (2002) Toxoplasma gondii: transmission, diagnosis, and prevention. Clin Microbiol Infect 8(10):634–640
46. Rosado JD, Rodriguez-Sosa M (2011) Macrophage migration inhibitory factor (MIF): a key player in protozoan infections. Int J Biol Sci 7(9):1239–1256
47. Butcher BA, Denkers EY (2002) Mechanism of entry determines the ability of toxoplasma gondii to inhibit macrophage proinflammatory cytokine production. Infect Immun 70(9):5216–5224. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=128277&Tool=Pmcentrez&Rendertype=Abstract
48. Werk R (1985) How does Toxoplasma gondii enter host cells? Rev Infect Dis 7(4):449–457. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/3898305
49. Khan IA, Matsuura T, Kasper LH (1994) Interleukin-12 enhances murine survival against acute toxoplasmosis. Infect Immun 62(5):1639–1642. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=186373&Tool=Pmcentrez&Rendertype=Abstract
50. Yarovinsky F (2014) Innate immunity to Toxoplasma gondii infection. Nat Rev Immunol 14:109–121. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/24457485
51. Flores M et al (2008) Macrophage migration inhibitory factor (MIF) is critical for the host resistance against Toxoplasma gondii. FASEB J 22(10):3661–3671. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2537436&Tool=Pmcentrez&Rendertype=Abstract
52. Terrazas CA et al (2010) Toxoplasma gondii: impaired maturation and pro-inflammatory response of dendritic cells in MIF-deficient mice favors susceptibility to infection. Exp Parasitol 126(3):348–358. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/20331989
53. Liesenfeld O (2002) Oral infection of C57BL/6 mice with Toxoplasma gondii: a new model of inflammatory bowel disease? J Infect Dis 185(Suppl 1):S96–S101
54. Cavalcanti MG et al (2011) MIF participates in toxoplasma gondii-induced pathology following oral infection. Plos One 6(9):e25259. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3178626&Tool=Pmcentrez&Rendertype=Abstract
55. De Oliveira Gomes A et al (2011) Effect of macrophage migration inhibitory factor (MIF) in human placental explants infected with Toxoplasma gondii depends on gestational age. Am J Pathol 178(6):2792–2801. Http://Dx.Doi.Org/10.1016/J.Ajpath.2011.02.005
56. Barbosa BF et al (2014) Susceptibility to Toxoplasma gondii proliferation in BeWo human trophoblast cells is dose-dependent of macrophage migration inhibitory factor (MIF), via Erk1/2 phosphorylation and prostaglandin E2 production. Placenta 35(3):152–162. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/24433846

57. Junqueira C et al (2010) The endless race between Trypanosoma cruzi and host immunity: lessons for and beyond chagas disease. Expert Rev Mol Med 12:e29
58. Parodi C, Padilla AM, Basombrío MA (2009) Protective immunity against Trypanosoma cruzi. Mem Inst Oswaldo Cruz 104:288–294
59. Aliberti JC et al (2001) Modulation of chemokine production and inflammatory responses in interferon-gamma-and tumor necrosis factor-R1-deficient mice during Trypanosoma cruzi infection. Am J Pathol 158(4):1433–1440
60. Gutierrez FRS et al (2009) The effects of nitric oxide on the immune system during Trypanosoma cruzi infection. Mem Inst Oswaldo Cruz 104(Suppl 1):236–245. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/19753479
61. Silva JS et al (1995) Tumor necrosis factor alpha mediates resistance to Trypanosoma cruzi infection in mice by inducing nitric oxide production in infected gamma interferon-activated macrophages. Infect Immun 63:4862–4867
62. Reyes JL et al (2006) Macrophage migration inhibitory factor contributes to host defense against acute Trypanosoma cruzi infection. Infect Immun 74(6):3170–3179
63. Terrazas CA et al (2011) MIF synergizes with Trypanosoma cruzi antigens to promote efficient dendritic cell maturation and IL-12 production via p38 MAPK. Int J Biol Sci 7(9):1298–1310
64. Cutrullis RA et al (2013) Elevated serum levels of macrophage migration inhibitory factor are associated with progressive chronic cardiomyopathy in patients with chagas disease. Plos One 8(2):e57181. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3579792&Tool=Pmcentrez&Rendertype=Abstract
65. Bosschaerts T et al (2009) Understanding the role of monocytic cells in liver inflammation using parasite infection as a model. Immunobiology 214(9–10):737–747. Http://Dx.Doi.Org/10.1016/J.Imbio.2009.06.010
66. Magez S et al (2004) P75 tumor necrosis factor-receptor shedding occurs as a protective host response during African trypanosomiasis. J Infect Dis 189(3):527–539
67. Stijlemans B et al (2010) Scrutinizing the mechanisms underlying the induction of anemia of inflammation through gpi-mediated modulation of macrophage activation in a model of African trypanosomiasis. Microbes Infect 12(5):389–399. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/20197106
68. Nishimura K et al (2011) Effect of Trypanosoma brucei brucei on erythropoiesis in infected rats. J Parasitol 97(1):88–93
69. Stijlemans B et al (2014) MIF contributes to Trypanosoma brucei associated immunopathogenicity development. Plos Pathog 10(9):e1004414. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=4177988&Tool=Pmcentrez&Rendertype=Abstract
70. Bosschaerts T et al (2010) Tip-DC development during parasitic infection is regulated by IL-10 and requires CCL2/CCR2, IFN-Γ and MyD88 signaling. PLoS Pathog 6(8):35–36
71. Peters NC et al (2008) In vivo imaging reveals an essential role for neutrophils in leishmaniasis transmitted by sand flies. Science 321(5891):970–974
72. Alexander J, Bryson K (2005) T helper (H)1/Th2 and Leishmania: paradox rather than paradigm. Immunol Lett 99(1):17–23
73. Herwaldt BL (1999) Leishmaniasis. Lancet 354:1191–1199
74. Kaye P, Scott P (2011) Leishmaniasis: complexity at the host-pathogen interface. Nat Rev Microbiol 9(8):604–615
75. Jüttner S et al (1998) Migration inhibitory factor induces killing of leishmania major by macrophages: dependence on reactive nitrogen intermediates and endogenous TNF-Alpha. J Immunol 161(5):2383–2390. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/9725234
76. Satoskar AR et al (2001) Migration-inhibitory factor gene-deficient mice are susceptible to cutaneous leishmania major infection. Infect Immun 69(2):906–911
77. Kar S, Metz C, Mcmahon-Pratt D (2005) Cd4+ T cells play a dominant role in protection against new world leishmaniasis induced by vaccination with the P-4 amastigote antigen. Infect Immun 73(6):3823–3827. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=1111832&Tool=Pmcentrez&Rendertype=Abstract

78. Kozaci DL et al (2005) [Investigation of serum macrophage migration inhibitor factor (MIF) levels in patients with cutaneous leishmaniasis.]. Türkiye Parazitol Der 29(3):145–148. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/17160809.
79. Santos-Oliveira JR et al (2011) Evidence that lipopolisaccharide may contribute to the cytokine storm and cellular activation in patients with visceral leishmaniasis. PLoS Negl Trop Dis 5(7):e1198. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=3134430&Tool=Pmcentrez&Rendertype=Abstract
80. Kamir D et al (2008) A Leishmania ortholog of macrophage migration inhibitory factor modulates host macrophage responses. J Immunol 180(12):8250–8261. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2668862&Tool=Pmcentrez&Rendertype=Abstract
81. Allen JE, Maizels RM (2011) Diversity and dialogue in immunity to helminths. Nat Rev Immunol 11(6):375–388
82. Boros DL, Pelley RP, Warren KS (1975) Spontaneous modulation of granulomatous hypersensitivity in schistosomiasis mansoni. J Immunol 114(5):1437–1441. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/804513
83. Stavitsky AB et al (2003) Blockade of macrophage migration inhibitory factor (MIF) in Schistosoma japonicum-infected mice results in an increased adult worm burden and reduced fecundity. Parasite Immunol 25(7):369–374. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/14521579
84. Rodríguez-Sosa M et al (2003) Macrophage migration inhibitory factor plays a critical role in mediating protection against the helminth parasite taenia crassiceps. Infect Immun 71(3):1247–1254. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=148860&Tool=Pmcentrez&Rendertype=Abstract
85. Patil S et al (2006) Proinflammatory cytokines in granulomas associated with murine cysticercosis are not the cause of seizures. J Parasitol 92(4):738–741. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/16995390
86. Baeza Garcia A et al (2010) Involvement of the cytokine MIF in the snail host immune response to the parasite Schistosoma mansoni. PLoS Pathog 6(9):e1001115. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2944803&Tool=Pmcentrez&Rendertype=Abstract
87. Pastrana DV et al (1998) Filarial nematode parasites secrete a homologue of the human cytokine macrophage migration inhibitory factor. Infect Immun 66(12):5955–5963. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=108754&Tool=Pmcentrez&Rendertype=Abstract
88. Falcone FH et al (2001) A Brugia malayi homolog of macrophage migration inhibitory factor reveals an important link between macrophages and eosinophil recruitment during nematode infection. J Immunol 167(9):5348–5354. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/11673551
89. Prieto-Lafuente L et al (2009) MIF homologues from a filarial nematode parasite synergize with IL-4 to induce alternative activation of host macrophages. J Leukoc Biol 85(5):844–854. Http://Www.Pubmedcentral.Nih.Gov/Articlerender.Fcgi?Artid=2691607&Tool=Pmcentrez&Rendertype=Abstract
90. Cho MK, Lee CH, Yu HS (2011) Amelioration of intestinal colitis by macrophage migration inhibitory factor isolated from intestinal parasites through toll-like receptor 2. Parasite Immunol 33(5):265–275. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/21204854
91. Park SK et al (2009) Macrophage migration inhibitory factor homologs of anisakis simplex suppress Th2 response in allergic airway inflammation model via CD4+CD25+Foxp3+ T cell recruitment. J Immunol 182(11):6907–6914. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/19454687
92. Park H-K et al (2012) Macrophage migration inhibitory factor isolated from a parasite inhibited Th2 cytokine production in pbmcs of atopic asthma patients. J Asthma 49(1):10–15. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/22149098
93. Greven D, Leng L, Bucala R (2010) Autoimmune diseases: MIF as a therapeutic target. Expert Opin Ther Targets 14(3):253–264. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/20148714

94. Tang F et al (2013) A DNA vaccine co-expressing Trichinella spiralis MIF and MCD-1 with murine ubiquitin induces partial protective immunity in mice. J Helminthol 87(1):24–33. Http://Www.Ncbi.Nlm.Nih.Gov/Pubmed/22221593
95. Angeli A et al (1999) Modulation by cytokines of glucocorticoid action. Ann N Y Acad Sci 876:210–220
96. Bloom BR, Bennett B (1966) Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science 153(3731):80–82
97. Calandra T et al (1995) MIF as a glucocorticoid-induced modulator of cytokine production. Nature 377(6544):68–71
98. David J (1966) Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc Natl Acad Sci U S A 56(1):72–77
99. Remold HG et al (1970) Studies on migration inhibitory factor (MIF): recovery of MIF activity after purification by gel filtration and disc electrophoresis. Cell Immunol 1:133–145