



The Role of MIF on Eosinophil Biology and Eosinophilic Inflammation

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Abstract

Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine that participates in innate and adaptive immune responses. MIF contributes to the resistance against infection agents, but also to the cellular and tissue damage in infectious, autoimmune, and allergic diseases. In the past years, several studies demonstrated a critical role for MIF in the pathogenesis of type-2-mediated inflammation, including allergy and helminth infection. Atopic patients have increased MIF amounts in affected tissues, mainly produced by immune cells such as macrophages, Th2 cells, and eosinophils. Increased MIF mRNA and protein are found in activated Th2 cells, while eosinophils stock pre-formed MIF protein and secrete high amounts of MIF upon stimulation. In mouse models of allergic asthma, the lack of MIF causes an almost complete abrogation of the cardinal signs of the disease including mucus secretion, eosinophilic inflammation, and airway hyper-responsiveness. Additionally, blocking the expression of MIF in animal models leads to significant reduction of pathological signs of eosinophilic inflammation such as rhinitis, atopic dermatitis, eosinophilic esophagitis and helminth infection. A number of studies indicate that MIF is important in the effector phase of type-2 immune responses, while its contribution to Th2 differentiation and IgE production is not consensual. MIF has been found to intervene in different aspects of eosinophil physiology including differentiation, survival, activation, and migration. CD4⁺ T cells and eosinophils express CD74 and CXCR4, receptors able to signal upon MIF binding. Blockage of these receptors with neutralizing antibodies or small molecule antagonists also succeeds in reducing the signals of inflammation in experimental allergic models. Together, these studies demonstrate an important contribution of MIF on eosinophil biology and in the pathogenesis of allergic diseases and helminth infection.

Keywords MIF · Eosinophil · Inflammation · Helminth · Allergy

Introduction

The capacity of supernatants from mitogen-activated lymphocyte to inhibit the random migration of macrophage *in vitro* led to the description of macrophage migration inhibitory factor (MIF), the first lymphokine activity discovered more than 50 years ago [1, 2]. MIF gene was cloned many years later in a functional screening assay that had the inhibition of monocyte migration as a read out [3]. An independent study using an

unbiased approach to characterize hormones secreted by the pituitary gland in response to LPS, identified MIF as a critical proinflammatory component of the LPS-induced lethality [4]. Macrophage is an important source of MIF, containing preformed protein and mRNA [5]. *In vitro*, MIF exhibits several proinflammatory functions, including the induction of TNF, IL-1 β , and nitric oxide (NO) production and increasing TLR4 expression by macrophages [6–10]. Low concentrations of glucocorticoids induce MIF production by macrophages that in turn counter-regulate the inhibitory effects of glucocorticoids on cytokine secretion induced by LPS [7]. A cytokine with chemokine-like functions, MIF promotes the migration of leukocytes through high affinity binding to CD74, a surface form of the MHC class II invariant chain Ii, and through the chemokine receptors CXCR2 and CXCR4 [11–13]. MIF also participates as a proinflammatory cytokine in both innate and adaptive immune responses to infection, contributing to the pathogenesis of inflammatory, metabolic, autoimmune, and allergic diseases [14–22].

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The Role of MIF in Eosinophil Biology

MIF is produced by a variety of cells and eosinophils constitute an important source of MIF in allergic inflammation and helminth infection [14]. Human circulating eosinophils have pre-formed MIF protein and upon stimulation with inflammatory mediators such as C5a or IL-5, secrete high quantities of MIF [23]. In vivo, eosinophils present in the inflamed tissue of patients with eosinophilic esophagitis have pre-formed MIF in the cytosol, constituting the main cell population expressing MIF in this disease [24]. A number of studies have shown important effects of MIF on eosinophil biology, including the induction of eosinophil maturation, chemotaxis, and activation (Fig. 1).

MIF directly promotes human eosinophil chemotaxis in vitro in a similar concentration range as that of the well-established eosinophil chemo-attractant eotaxin/CCL11 [24]. MIF's chemotactic effect can be inhibited by ISO-1, a MIF antagonist, as well as by AMD3100, an antagonist of MIF's receptor CXCR4. MIF is also chemotactic for mouse eosinophils in a mechanism dependent on CXCR2 and CXCR4 [25, 26]. Corroborating these in vitro data, intrapleural administration of recombinant MIF in mice induces the recruitment of eosinophils [25] and intra-nasal administration of MIF to mice increases the number of eosinophils in the esophagus [24]. The main role of MIF in eosinophil recruitment in vivo is reinforced by using strategies such as knocking out *Mif* in mice or blocking MIF or its receptors (ex. CD74, CXCR4) which ultimately leads to a profound reduction of eosinophil numbers in inflamed tissues in experimental models of allergic and parasitic diseases [24–35].

Eosinophils may develop cytoplasmic inclusions known as lipid bodies upon inflammatory stimulus [36]. These lipid-rich cytoplasmic inclusions, derived from endoplasmic reticulum, contain membrane and ribosome organelles and play an important role in arachidonic acid metabolism [36]. Human eosinophils stimulated with recombinant MIF develop increased numbers of cytoplasmic lipid bodies and enhanced production of CCL11 and leukotriene C4 [25]. The lipid body generation induced by MIF on eosinophils is dependent on the cell surface receptor CD74 expression. MIF-induced CCL11 acts in an autocrine/paracrine way contributing to the generation of lipid bodies dependent on eosinophil CCR3 expression [25]. Conversely, stimulation of human eosinophils with CCL11 induces biogenesis of lipid bodies, an effect reverted by anti-CD74 neutralizing antibody. Similarly, treatment with CCL11 reduces lipid bodies in eosinophils from *Mif*^{−/−} mice compared to eosinophils from WT. Suboptimal concentrations of CCL11 and MIF have a synergistic effect to induce the generation of lipid bodies [25]. These results indicate that MIF and CCL11 cooperate in the activation of eosinophils.

The terminal differentiation of committed bone-marrow eosinophil precursors can be mediated by a cooperation involving IL-5, IL-3, and GM-CSF with IL-4 and CCL3 [37, 38]. To understand if MIF participated in eosinophil maturation, bone marrow from *Mif*^{−/−} mice was studied in vitro and shown to be defective in generating eosinophils even in the presence of high concentrations of IL-5 [26]. Additionally, inclusion of rMIF in *Mif*^{−/−} bone marrow cultures fully restores the ability of IL-5 to promote accumulation of eosinophils to the extent achieved in WT. Moreover, data shows that in the absence of MIF, eosinophil precursors are more prone to

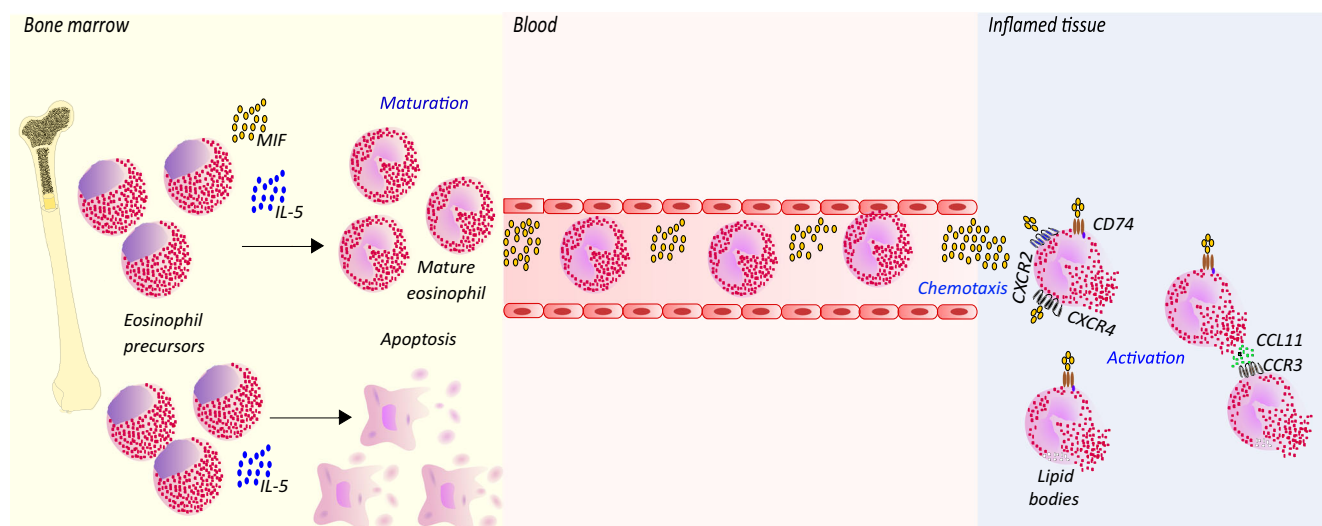


Fig. 1 MIF acts on eosinophils, leading to an increase of their numbers in the tissues during inflammation by at least two concurrent mechanisms. First, MIF licenses IL-5 to induce eosinophilopoiesis in the bone marrow by promoting the escape from death of eosinophil precursors, according to in vitro data. Second, MIF provides an essential help to eosinophil

chemotaxis in a CD74, CXCR2, and CXCR4-dependent manner. MIF engagement of CD74 directly improves the secretion of CCL11 and lipid bodies by eosinophils. Synergistically, MIF-induced CCL11 improves the synthesis of lipid bodies by eosinophils in an autocrine/paracrine manner after binding to CCR3

die by apoptosis, since treatment of *Mif*^{-/-} cell cultures with the pan-caspase inhibitor zVAD restores the number of eosinophils accumulated in the presence of IL-5 to that found in WT controls [26]. However, in mature eosinophils the anti-apoptotic effect of MIF is modest when compared with GM-CSF [39]. These results indicate that MIF acts as a cofactor necessary to allow optimal eosinophilopoiesis through the protection of eosinophils, during terminal differentiation induced by IL-5, from programmed cell death. These results also suggest that reduced blood and tissue eosinophilia of *Mif*^{-/-} mice upon type-2 immune responses could in part be due to a defect in eosinophilopoiesis.

Critical Role of MIF in the Pathogenesis of Allergic Inflammation

MIF in Allergic Asthma and Rhinitis

Clinical studies with asthmatic and atopic dermatitis patients in the late 1990s demonstrated that MIF participates in allergic processes [40–43]. Asthmatic patients presented higher MIF concentrations in the bronchoalveolar lavage (BAL) and sputum, compared to healthy controls [42, 43]. Airway epithelial cells, macrophages, mast cells, and Th2 lymphocytes were shown to produce and secrete MIF, likely contributing to the MIF produced during allergic episodes [5, 29, 44, 45]. Production and secretion of MIF by human eosinophils indicates that these cells are one of the several potential sources of MIF in asthmatic patients [42]. Overall, these studies added MIF to a long list of inflammatory mediators found in atopic patients with allergic asthma and produced by cells involved in this complex inflammatory condition. Moreover, functional polymorphisms in the promoter region of MIF gene in humans have been associated with increased risk of atopy, reinforcing the role of MIF in the pathogenesis of allergic diseases such as asthma and atopic dermatitis [27, 46, 47].

Experimental studies of atopic asthma demonstrated that MIF is increased in the BAL fluid of challenged animals and contribute to the lung allergic inflammatory response, including the accumulation of eosinophils, mucus hypersecretion, and airway hyperreactivity (AHR) [27–29, 48] (Figs. 2 and 3). Increased MIF expression was also observed in epithelial cells and infiltrating leukocytes in the lungs of mice with chronic asthma, a model characterized by airway remodeling and increased TGF- β 1 expression [30]. Using ovalbumin to induce experimental asthma, it has been shown that MIF affects the allergic response in multiple ways; however, the precise mechanisms associated with the pathogenic role of MIF in asthma are still not well understood.

The lack of characteristic features of asthma due to the absence of MIF was initially associated with its participation in the induction of the adaptive immune response, as indicated

by reduced antigen-specific lymphocyte activation, Th2 cytokine, and IgE production [27, 29, 32]. The reduced activation of antigen-specific CD4⁺ T cells and reduced production of Th2 cytokines observed in *Mif*^{-/-} compared to WT mice in an asthma model was then attributed to an impaired antigen-presentation function of DCs in the absence of MIF [27]. A different study, however, demonstrated that reconstitution of ovalbumin-sensitized *Mif*^{-/-} mice with mast cells from WT mice restored the recruitment of eosinophils to the airways and the serum concentrations of IgE, indicating a role of mast cell-derived MIF, but not from DCs or splenocytes, in the induction of the allergic response [29].

Using epicutaneous sensitization with ovalbumin in the absence of adjuvant, *Mif*^{-/-} mice was shown to have reduced numbers of eosinophils in the lung, antigen-induced T cell proliferation, Th2 cytokine production, total IgE, and ovalbumin-specific IgG1 serum concentrations upon intranasal challenge compared to WT mice, suggesting a contribution of MIF to the sensitization and the effector phases of the adaptive response [32]. Moreover, *Mif*^{-/-} mice present increased numbers of CD4⁺Foxp3⁺ T regulatory cells (Tregs) in draining lymph nodes [32]. Lack of the MIF receptor CD74 impairs the generation of a Th2 response to epicutaneous sensitization. In this model, MIF produced by T cells, but not by antigen-presenting cells, is critical for T cell activation. Independent of the genotype of the antigen presenting cells used, *Mif*^{-/-} DO11.10 TCR transgenic T cells present reduced proliferation and IL-2 production when compared with DO11.10 TCR transgenic T cells derived from WT mice [32].

Other groups found that lack of MIF impairs the effector phase of the allergic response but not the priming of T lymphocytes. *Mif*^{-/-} mice immunized with ovalbumin and alum and challenged with ovalbumin have reduced AHR, tissue eosinophilia, mucus metaplasia and lung inflammatory mediators (IL-13, IL-5, CCL11, and Cys-leukotrienes) despite high serum IgE and Th2 cytokine concentrations in draining lymph nodes [28]. Similarly, treatment of mice or rats with anti-MIF antibodies in the challenge phase is sufficient to impair AHR and the increase eosinophilia without affecting Th2 cytokines and IgE production [28, 31, 48]. Transgenic mice over-expressing Thioredoxin-1 have reduced production of MIF compared to WT mice and abrogation of the cardinal features of asthma, including IL-13 and CCL11 amounts in the lungs, despite similar systemic Th2 response and IgE concentrations [49]. Thioredoxin-1, when expressed on the cell surface, binds MIF with high affinity and promotes MIF internalization, suggesting a possible mechanism by which Thioredoxin-1 inhibits MIF-mediated inflammation [50]. MIF is part of the thioredoxin family of proteins, displaying thiol reductase activity [51–53].

MIF is also essential for eosinophil activation demonstrated by a marked reduction of eosinophil recruitment, lipid body generation, and LTC₄ production in tissue eosinophils in *Mif*

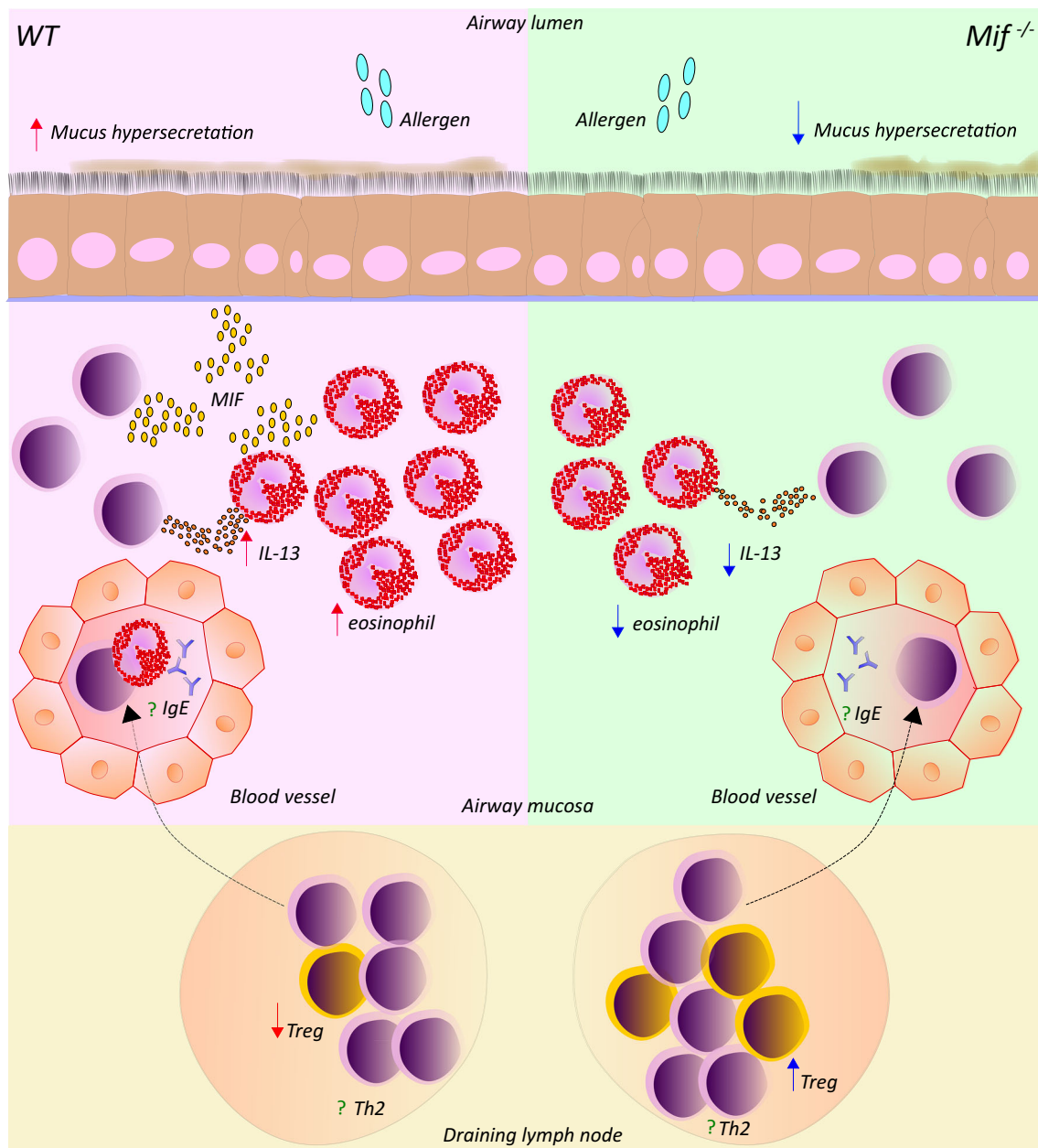


Fig. 2 MIF accumulates in the bronchoalveolar lavage from asthmatic patients and allergen challenged mice. The use of *Mif*^{-/-} mice elucidates the key role of MIF in the development of asthma features. Upon allergen challenges *Mif*^{-/-} mice have less eosinophils, IL-13 levels, and mucus

production in the airways, compared to wild-type (WT) mice. Besides, eosinophilia is reduced in *Mif*^{-/-} mice. In draining lymph nodes, *Mif*^{-/-} mice have more Treg cells than WT mice

–/– mice compared with WT, in a mouse model of pulmonary allergic inflammation [25]. The in vivo treatment with recombinant MIF triggers eosinophil recruitment to the lung and synthesis of LTC₄ by newly formed lipid bodies. Together, these results indicate that the contribution of MIF to allergic inflammation occurs with or without impairment of the antigen-specific immune response. At present, it is unclear why in some studies the lack of MIF abrogates Th2 differentiation while in others MIF is essential to the asthma inflammation but not to the activation of antigen-specific Th2 cells

or to the increase of IgE amounts. These discrepancies could be related to differences in the experimental protocols, genetic background, and animal microbiome in the different studies.

A hallmark of chronic inflammation and type-2-mediated pathologies is tissue remodeling. The progressive structural changes in asthmatic patients include airway smooth muscle proliferation, thickness of the subepithelial reticular basement membrane, goblet cell metaplasia, mucus plugs, and lung collagen deposition which cause cumulative loss of pulmonary function [54]. Although the contribution of inflammation in

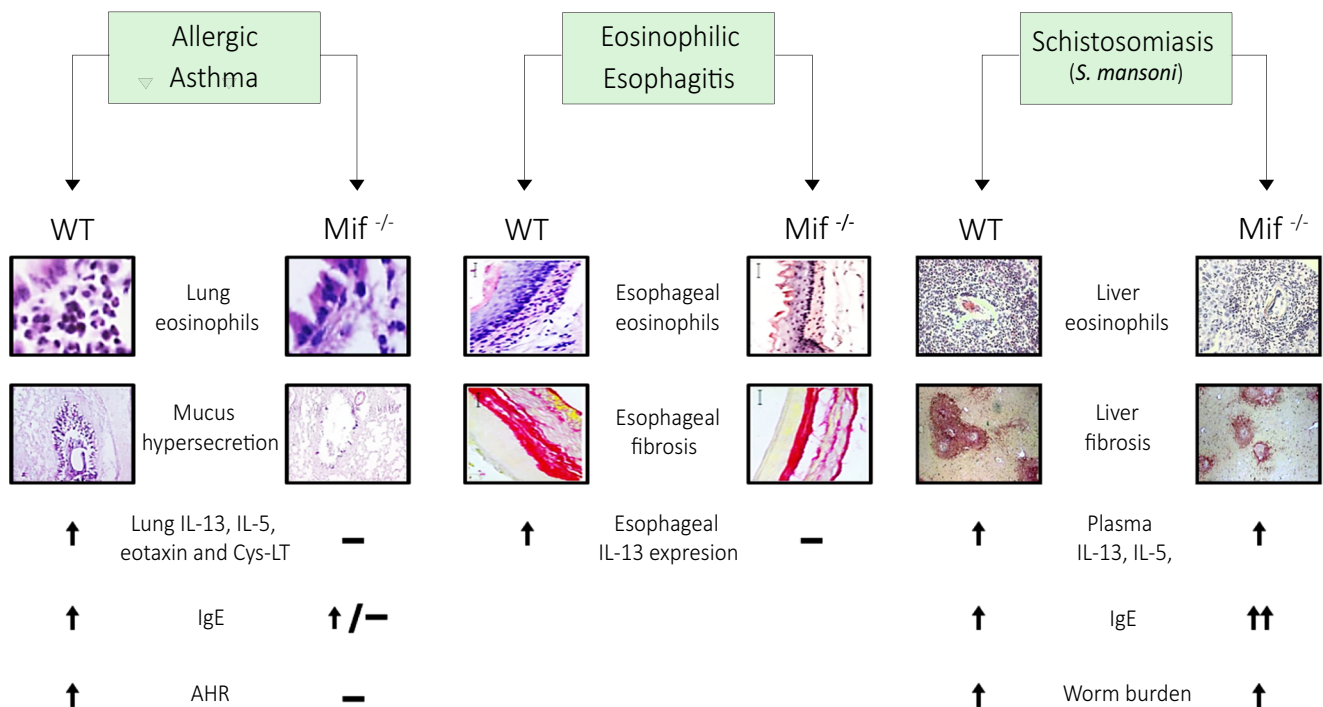


Fig. 3 In asthma models, allergen challenges of *Mif*^{-/-} mice have a minor impact on lung inflammation and remodeling, as indicated by the reduced numbers of eosinophils, IL-13, IL-5, CCL11, and Cys-LT levels, and mucus hypersecretion in the lungs of *Mif*^{-/-} mice compared to wild-type (WT) mice. Data on the impact of MIF in seric IgE levels are not conclusive in asthma models. *Mif*^{-/-} mice do not develop airway hyperreactivity (AHR) after several allergen challenges and lung function test using bronchoconstrictors. In eosinophilic esophagitis models, *Mif*^{-/-} mice present decreased numbers of eosinophils, IL-13

expression and fibrosis in the esophagus compared to WT mice. In models of schistosomiasis caused by the eggs of *Schistosoma mansoni*, *Mif*^{-/-} mice present less eosinophils in the liver than WT mice, after infection. Despite this, IL-13 and IL-5 increased levels, fibrosis and worm burden are presented in the same extent in WT and *Mif*^{-/-} mice, while seric IgE levels are increased in *Mif*^{-/-} mice. The representative histological figures in a, b, and c are from published data of Magalhães et al. [28], De Souza et al. [24], and Magalhães et al. [26], respectively

tissue remodeling is still under dispute, previous studies indicate that eosinophils may play an important role to tissue remodeling in allergic conditions [54, 55]. However, eosinophils are not essential for remodeling and inflammation in a chronic model of asthma induced by house dust mite (HDM) [56]. HDM is considered a clinically relevant allergen associated with asthma pathogenesis, including the activation of lung epithelial cells, dendritic cells and basophils that trigger cytokine production that on its turn affects innate lymphoid cells and T CD4⁺ T cells [57, 58]. Treatment with ISO-1, a MIF small molecule antagonist, causes a significant reduction in lung eosinophil numbers and airway remodeling in a mouse model of chronic asthma induced by long-term sensitization and challenge with ovalbumin [30]. The protective effect of ISO-1 on airway remodeling is similar to that of dexamethasone treatment. The inhibitory effect of ISO-1 on TGF- β expression and eosinophil infiltration in the lung upon ovalbumin sensitization might have contributed to inhibition of airway remodeling observed in mice [30]. Compared to WT mice, *Mif*^{-/-} have reduced eosinophil infiltration and TNF expression in nasal mucosa induced by ovalbumin immunization and intranasal challenge [33]. Importantly, MIF expression is also increased in biopsy specimens of the nasal mucous

membrane, especially in the infiltrating eosinophils of human patients with atopic rhinitis [59].

MIF Contributes to the Pathogenesis of Atopic Dermatitis and Conjunctivitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease, associated with various factors, including immunological abnormalities and exposure to allergens that contribute to the pathogenesis and development of eczematous skin lesions and intense itching [60, 61]. AD usually starts early in life, occurs in episodes of acute flares and is usually related with other allergic conditions such as asthma, rhinitis, and food allergy [60]. The increased exposure to environmental stimuli due to epidermal barrier defects is considered important to the pathogenesis. As other allergic disorders, AD courses with a type-2 response with infiltration of Th2 cells and eosinophils into skin lesions. In AD, the Th2 cells are the main producers of IL-4, IL-5, and IL-13, which, together with CCL11 are keys to the pathology [60, 62].

Inflammatory skin lesions and sera from AD patients have high expression of MIF mRNA and protein [41, 63]. The quantities of MIF in stratum corneum (sc) were increased in

skin lesions from patients compared to healthy control samples [64]. An inverse correlation is observed regarding the serum concentrations of MIF and clinical improvement in AD patients [40]. Overall, these studies indicate that MIF contributes to the pathogenesis and might be a marker of disease severity [40, 64].

MIF contributes to the induction of a type-2 response and eosinophil recruitment to the skin in mouse models of AD [34]. Mice overexpressing MIF also have high Th2 cytokines and eosinophilia in the skin when immunized with ovalbumin compared to WT mice. Lack of MIF abrogates the expression of inflammatory cytokines and skin eosinophilic infiltration upon repeated epicutaneous challenge with ovalbumin when compared to WT mice [34]. Similarly, a MIF-DNA vaccine that elicited the generation of endogenous anti-MIF antibodies impairs the inflammatory skin manifestations in a mouse model of AD induced by ovalbumin immunization and challenge [65].

An essential role of MIF in atopic conjunctivitis has been shown using relevant allergens such as ragweed pollen or Japanese cedar pollen [35]. In this model, MIF transgenic mice have increased mRNA expression of type-2 cytokines and infiltrating eosinophils when compared with WT mice. Fibroblasts overexpressing MIF have higher expression of CCL11 upon treatment with IL-4 compared to WT mice, while in these conditions fibroblasts from *Mif*^{-/-} mice showed negligible expression of CCL11 [35].

MIF Has a Central Role in Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic disease characterized by the presence of infiltrating eosinophils in the esophagus and upper gastrointestinal symptoms that vary with age and can include fibrostenotic complications [66]. The disease has a typical type-2 immune response triggered by environmental factors such as food and aeroallergens, and is responsive to topical glucocorticoids and dietary elimination therapy. The majority of patients with EoE have an atopic phenotype [67]. In fact, several evidences support an allergic etiology as an underlying mechanism for EoE. Patients with EoE have a high incidence of concurrent atopic disease. Recent evidence shows that EoE is correlated with high prevalence of asthma and AHR. Sensitization to cutaneous, ingested, and/or inhaled allergens is likely necessary in the development of EoE, and in some patients, seasonal allergens may play a role. The esophageal eosinophilia is considered the main characteristic of human EoE, but the mechanisms involved in cell accumulation in the tissue and the exact role of eosinophils in disease pathogenesis are not fully understood. EoE patients have an increased deposition of sub-epithelial collagen fibers and thickening of the basal cell layer due to an increased proliferation of epithelial cells [68, 69]. Evidence of release of eosinophil granule components has been directly observed in EoE biopsies; therefore, eosinophils most likely have an effect on

epithelial cell damage in EoE [66, 67]. In addition, eosinophils also have the potential for production of diverse cytokines such as IL-4, IL-5, and IL-13; the chemokine CCL11 [67]; MIF [24]; and many others.

MIF expression is remarkably high in biopsy samples from EoE patients, detected in cells of the immune system, especially eosinophils, and correlates with the number of esophageal eosinophils [24]. High MIF expression also occurs in esophageal samples of gastroesophageal reflux disease (GERD) patients compared to controls. Type-2 immunity predominates in EoE inflammatory response in opposition with the predominant type-1 response in GERD [70], thus generating an environment in which eosinophils are recruited to and persist within the inflamed mucosa. Since eosinophils are the main producers of MIF in EoE, it is unlikely that MIF triggers the initial inflammatory response, rather participating in the effector phase of the disease.

Murine models using sensitization and oral challenges with ovalbumin, peanut, or inhaled ovalbumin, *aspergillus* or dust mite antigen lead to IL-5-, IL-13-, and CCL11-dependent esophageal eosinophilia [66]. *Mif*^{-/-} mice are protected in a model of allergic EoE, showing less eosinophilic infiltration, collagen deposition and IL-13 expression compared to the WT mice [24]. MIF is chemotactic to eosinophils in a mechanism that requires CXCR4 [24], the chemotactic receptor of SDF-1a/CXCL12 [13, 71]. Treatment with recombinant MIF promotes tissue eosinophilia and collagen deposition in ovalbumin-sensitized mice, while treatment with anti-MIF monoclonal antibody or with a CXCR4 antagonist (AMD3100, Plerixafor) during the challenge phase can prevent the signs of EoE. Both eosinophils and basophils express CXCR4 [72, 73]. These cells are considered fundamental to the pathogenesis of EoE [74, 75], thus suggesting a role for MIF/CXCR4 axis on basophil function and in the pathogenesis of EoE. It will be important to discriminate the selective contribution of MIF and of SDF-1a/CXCL12, the cognate ligand of CXCR4, on EoE. These findings indicate that blocking MIF or the CXCR4 receptor constitute a putative strategy to treat patients with EoE. AMD3100 is currently approved by the FDA for short-term treatment, while a low-dose and long-term treatment protocol presented promising results [76].

MIF and Helminth Infestation

A number of studies characterized the role of MIF in helminth infection, a condition usually characterized by a type-2 immune response. *Mif*^{-/-} mice have reduced granuloma size upon infection with *S. mansoni*, but no impairment on type-2 immunity compared to WT mice [26]. Blockade of MIF with antibody treatment, however, has no effect in granuloma formation in mice infected with *Schistosoma japonicum* [77].

Mif^{-/-} mice infected with *S. mansoni* have granulomas with fewer eosinophils, a phenomenon that is paralleled by reduced eosinophilopoiesis, indicating that MIF orchestrates bone marrow eosinophil differentiation and migration to granulomas. Upon *S. mansoni* infection, *IL-5*^{-/-} mice or in *IL-13*/*IL-4* double-deficient mice have impairment of the Th2 polarization, smaller granulomas, reduced eosinophilopoiesis and fibrosis [78, 79]. These studies confirm the pro-fibrotic role of *IL-13*. *Mif*^{-/-} mice present similar fibrosis compared to WT mice infected with *S. mansoni* [26], contrasting with reduced tissue remodeling in *Mif*^{-/-} mice in allergic models of asthma and eosinophilic esophagitis, in which there is a significant reduction in *IL-13* [24, 30] (Fig. 3).

Mif^{-/-} mice were susceptible to the murine cysticercosis caused by the helminthic parasite *Taenia crassiceps* and developed significantly higher parasite loads compared to WT mice [80]. Treatment of mice with anti-MIF neutralizing antibodies also increases parasite burden and fertility on *S. japonicum* infection [77]. In *S. mansoni* infection, WT and *Mif*^{-/-} mice have similar numbers of adult forms and eggs [26]. Eosinophils are considered efficient to kill the *S. mansoni* in vitro [81] and to invade unhealthy schistosomes in vivo [82], suggesting that eosinophils are effector cells against the parasite. Mouse lineages deficient in eosinophils, however, show no major change in worm burden or liver fibrosis upon *S. mansoni* infection [83]. *Mif*^{-/-} infected with *Nippostrongylus brasiliensis* have reduced parasite burden in the intestine and increased Th2 response in the draining lymph nodes [84]. The increased type-2 immunity was associated to a reduction in *IL-6* production in T CD4 *Mif*^{-/-} cells. Thus, the variable outcomes of helminthic infections in mice lacking MIF might reflect the susceptibility of these parasites to the different defense mechanisms that MIF contributes, which are currently poorly understood.

Orthologues of vertebrate MIF were identified in a number of infectious agents, especially parasites, and are likely involved in escape mechanisms [85–87]. In fact, *Brugia malayi* has a MIF orthologue that influences eosinophil function and other aspects of the inflammatory response that overall facilitate parasite survival [88, 89]. Treatment with *Brugia malayi*-MIF and *IL-4* induces alternatively activated macrophages [90]. Although vertebrate MIF is mainly associated with pro-inflammatory responses, treatment of monocytes with MIF orthologues from *Strongyloides ratti* triggers the production of *IL-10*, suggesting a role of the secreted parasite MIF in escape mechanisms [91]. Similarly, MIF produced by the nematode *Anisakis simplex* causes an increase in *IL-10* production by a mechanism dependent on TLR2 and associated with an increased recruitment of Tregs [92–94]. It is tempting to speculate that MIF orthologues compete with host MIF, thus modulating the host immune response in favor of parasite invasion/maintenance. The exact molecular and cellular mechanisms involved in this effect of each MIF orthologue require further investigations.

Conclusion and Perspective

Several studies in the past years demonstrated that MIF plays a critical role in type-2 inflammatory responses, including allergic diseases and helminth infection. In experimental models of atopic diseases, the lack of MIF is associated with a profound reduction of the hallmarks of inflammation such as leukocyte infiltration, inflammatory mediator production, and tissue dysfunction. These studies indicate that MIF contributes to the effector phase of the inflammatory response, while its role in the Th2 differentiation and IgE production is less consensual. Blockage of MIF after the immunization and during the challenge phase is effective to abrogate the signs of disease in experimental models of allergic diseases including asthma, dermatitis, and eosinophilic esophagitis. In recent years, it has been demonstrated that secretion of cytokines such as *IL-33*, *IL-25*, and TSLP by epithelial cells triggers the immune response to allergens [58]. These cytokines recruit and activate innate lymphoid cells 2 (ILC2) and dendritic cells culminating in the differentiation of Th2 cells, considered central to the pathogenesis of allergic diseases. In order to better define the specific participation of MIF in the genesis of allergic diseases, it will be essential to use better experimental models with complex and clinically relevant allergens, including house dust mite and mouse strains with cell-specific deletion of MIF and its receptors. This will allow to define the role of different cell sources and targets of MIF in selective disease models. Finally, clinical trials targeting MIF through the use of anti-MIF neutralizing antibodies, MIF antagonists and CXCR4 antagonist will help to define the importance of MIF in the pathogenesis of human allergic diseases.

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Compliance with Ethical Standards This work is in accordance with the ethical standards of the COPE guidelines.

Conflict of Interest The authors declare that they have no conflict of interests.

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