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# Macrophage migration inhibitory factor (MIF): a promising biomarker

**Gerrit Grieb**[1,2,3,§], **Melanie Merk**[1], **Jürgen Bernhagen**[3], and **Richard Bucala**[1]

[1] Departments of Medicine, Pathology, Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06520, USA

[2] Department of Plastic Surgery and Hand Surgery, Burn Center, Medical Faculty, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany

[3] Department of Biochemistry and Molecular Cell Biology, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany

## Abstract

Macrophage migration inhibitory (MIF) factor is an immunoregulatory cytokine whose effect on arresting random immune cell movement was recognized several decades ago. Despite its historic name, MIF also has a direct chemokine-like function and promotes cell recruitment. Multiple clinical studies have pointed to the utility of MIF as a biomarker for different diseases that have an inflammatory component; these include systemic infections and sepsis, autoimmune diseases, cancer, and metabolic disorders such as type 2 diabetes and obesity. The identification of functional promoter polymorphisms in the MIF gene (*MIF*) and their association with the susceptibility or severity of different diseases has served not only to validate MIF's role in disease development but opened the possibility of using *MIF* genotype information to better predict risk and outcome. In this article, we review the clinical data of MIF and discuss its potential as a biomarker for different disease applications.

## 1. Introduction

Macrophage migration inhibitory factor (MIF) is a pleiotropic inflammatory mediator that is considered the first cytokine activity to be reported [1-3]. MIF was cloned, purified, and its activity characterized at the molecular level in 1993 [4]. MIF is structurally unique; its monomeric molecular weight is 12.5 kDa, with two antiparallel alpha-helices and six beta-pleated sheets forming an extended secondary structure of the molecule. Biophysical studies indicate that in its active form, MIF is a homotrimeric molecule with topologic homology to only one other mammalian protein, the enzyme D-dopachrome-tautomerase [5].

Despite its eponymic activity, MIF also has a chemokine-like function and promotes the directed migration and recruitment of leukocytes into infectious and inflammatory sites [6]. MIF is produced by a variety of cell types that in addition to immune cells such as monocytes/macrophages, B- and T-cells include endocrine, endothelial, and epithelial cells [7]. MIF is stored in preformed, cytoplasmic pools and is rapidly released in response to such stimuli as microbial products, proliferative signals, and hypoxia [8-11]. One of the earliest physiologic functions described for MIF is to counter-regulate glucocorticoid suppression of immune cell responses [12], which is important for the regulation of the

§ Corresponding author: Department of Medicine and Pathology, Yale University School of Medicine, New Haven, CT 06520, USA Tel.: 203 737 5103, Fax: 203 785 7053 gerritgrieb@gmx.de .

systemic inflammatory response in settings such as invasive stress or acute illness when adrenal glucocorticoid levels are high. MIF also plays a pivotal upstream role in sustaining immune cell survival by inhibiting activation-induced apoptosis. This effect serves to provide for optimal and, in some pathologic circumstances, excessive, inflammatory responses [13].

MIF binds to CD74, a type II transmembrane protein [14], inducing its phosphorylation and the recruitment of CD44 [15], which then activates SRC family non-receptor tyrosine kinases, leading ultimately to ERK1/2 phosphorylation. Notably, this receptor complex may be associated with the CXCR2 or CXCR4 chemokine receptors, which also bind MIF and mediate the inflammatory pathogenesis of experimental atherosclerosis [6]. Given these upstream actions in the inflammatory cascade, it is not surprising that MIF plays a central role in different acute and chronic inflammatory diseases as well as in cancer. We review herein the potential role of MIF as a biomarker for different clinical applications.

## 2. MIF in infectious diseases and sepsis

MIF normally circulates at levels between 2-10 ng/ml in human plasma, but fluctuates in a diurnal rhythm that appears to reflect neuroendocrine control [16]. Plasma MIF concentrations can be elevated to extremely high levels in different inflammatory disorders. The first indications that MIF might be involved in systemic infection and in sepsis, and might serve as a biomarker, were provided by Bernhagen et al. in the early 90s, who described MIF to be a major protein secreted by the pituitary gland upon LPS stimulation [4]. Subsequently, the activated macrophage as well as other cell types were shown to be major producers of MIF upon inflammatory activation [9, 17, 18].

First evidence for a role for MIF in sepsis and septic shock was given by Calandra et al., who demonstrated high circulating concentrations of MIF in septic patients and even higher MIF levels in those subjects with septic shock [19]. A subsequent study by Lehmann et al. examined MIF in 19 septic and 18 critically ill post-surgical non-septic patients. A four to five fold increase of MIF could be observed in both groups compared to the healthy controls [20]. Thus, MIF appeared to be a biomarker for critical illness but not necessarily sufficient to differentiate between infectious and noninfectious causes of systemic inflammation. Bozza et al. recently confirmed high levels of MIF in sepsis based on a study of 42 patients. These authors concluded that MIF serves as an early indicator for poor outcome of critically ill patients [21]. Tannus-Furtado et al. analyzed MIF levels in septic patients after cardiac surgery, which represents a more homogeneous study population. The study included 49 patients who developed sepsis between the second and eighth postoperative day. MIF levels were significantly higher in patients with positive blood cultures ($p<0.001$), and thus MIF appeared to be a good predictor of culture-proven bacterial infections after cardiac surgery [22]. Notwithstanding these reports, some observations have questioned the value for MIF as a marker of systemic infection or sepsis. Kofoed and colleagues performed a prospective study of 96 patients with bacterial infection. 58 patients suffered from a respiratory infection (mostly *Streptococcus pneumonia*), 25 from a urinary infection (mostly *E. coli*), 16 from a gastrointestinal infection (mostly *Campylobacter jejuni*), 8 from a skin soft tissue infection (*Streptococcus* or *Staphylococcus*), 5 from a central nervous infection (e.g. *Neisseria menigitidis*) and 9 from infections without focus. MIF's role as an infectious marker in this study was comparable but not superior to C-reactive protein (CRP) or procalcitonin (PCT), which exhibited more favorable capabilities for detecting infection (positive predictive values; MIF: 0.73 CRP: 0.79, PCT: 0.80) [23].

Two independent studies have focused on sepsis originating from particular infectious agents. Sprong et al. investigated circulating MIF levels and their correlation with other

biomarkers and clinical parameters in 20 patients with *Neisseria mengitidis* infection. Emonts et al. additionally studied two clinical cohorts of 145 individuals infected with *N. mengitidis*, one consisting of adults and one of children [24, 25]. Each of these studies revealed high serum levels of MIF in *N. mengitidis*-associated sepsis and a strong correlation between MIF and disease severity ($p<0.001$). In a further analysis of sepsis patients, Gando et al. compared 20 patients with disseminated intravascular coagulation (DIC) with 28 non-DIC septic patients and concluded that elevation of MIF and TNF-α were both related to poor prognosis and mortality (OR 1.016, $p<0.04$) [26]. The potential for combining MIF with other biomarkers was considered in a recent study of 23 patients with burn-related sepsis symptoms. The tandem determination of both procalcitonin and MIF predicted a fatal outcome in severely burned patients when compared to survivors [27].

A recent report has provided evidence for a role of MIF as a biomarker in central nervous system infection as serum levels appeared to correlate with severity of meningitis [28]. Rahman et al. also have suggested the prognostic utility for MIF in predicting acute pancreatitis and pancreatic necrosis [29].

Urinary levels of MIF, which most likely reflect production from infiltrating inflammatory cells in the kidney, also has been studied as a biomarker of renal infection. In an attempt to develop an easy assessment for distinguishing acute pyelonephritis from acute cystitis in children, Otukesh et al. tested 33 pediatric patients for urine MIF [30]. The study revealed that a high urine MIF/creatinine ratio is associated with acute pyelonephritis.

Measurements of intracellular MIF in different circulating cell types also have been studied in septic patients. Among pro-inflammatory cytokines, MIF is distinguished by being present in many cell types in pre-formed, intracytoplasmic pools [9]. Using flow cytometry analysis, MIF was found to be elevated simultaneously in lymphocytes, B-cells, macrophages and granulocytes in patients with severe sepsis when compared to healthy control individuals [31].

## 3. MIF in autoimmune diseases

One of the first clinical studies regarding MIF expression in autoimmunity was in rheumatoid arthritis patients [32]. Increased levels of MIF were detectable not only in the circulation and synovial fluid, but also within inflamed synovial tissue [32]. These findings were confirmed by Onodera and colleagues [33] who examined MIF levels in synovial fluid collected from 25 patients with rheumatoid arthritis. High elevated MIF concentrations also were observed when compared with osteoarthritis patients and healthy volunteers [33]. Of note, anti-MIF was found to significantly reduce the spontaneous production of TNF by isolated synoviocytes in vitro; this provided first evidence for a high apex position of MIF in the inflammatory cascade that leads to intra-articular cytokine production and destructive changes within the joint. In addition, Morand et al. demonstrated that in athroscopically obtained biopsies from rheumatoid arthritis patients' synovium, MIF correlated strongly with the immunohistological scoring of disease activity ($r=0.94$, $p<0.001$) [34].

In a recent study, Kim et al. focused on MIF's role in the neo-angiogenic changes that support the development of invasive pannus. These authors found high MIF levels in both serum and synovial fluid [35] and furthermore demonstrated a high correlation with VEGF, which is an important endothelial cell growth factor. These observations were used to support the conclusion that MIF also has a role in promoting angiogenic processes in rheumatoid arthritis [35].

High MIF production in autoimmune kidney diseases was first described by Lan et al. in studies of an experimental rat model [36]. Taniguchi and colleagues subsequently reported

higher MIF production in the kidney tissue of IgA nephropathy patients compared to healthy controls [37]. In accordance with this finding, the same group found high MIF in kidney tissue of anti-neutrophil cytoplasmic antibody-associated (ANCA) glomerulonephritis [38]. The association between MIF and autoimmune kidney disease was further investigated by Bruchfeld et al., who studied 257 patients with chronic kidney disease different etiologies. They suggested that high MIF levels in these patients are closely linked to endothelial activation and that MIF might play a role in the vascular disease associated with chronic kidney disease [39].

The spectrum of autoimmune diseases that involve MIF is potentially large and diverse. High MIF levels were found in patients with SLE [40], systemic sclerosis [41], Wegener's granulomatosis, and relapsing polychondritis [42]. In the case of SLE, MIF levels may be associated with glucocorticoid therapy [40], which is especially interesting given that glucocorticoids have the ability to induce MIF expression from immune cells [12, 43]. MIF counter-regulates the immunosuppressive action of steroids and may play a role in the development of steroid resistance in asthma or autoimmune diseases [44]. Nevertheless, establishing a clinical correlation between MIF levels and either steroid therapy or steroid resistance is problematic given that those patients who receive high doses of glucocorticoids are also those with the highest levels of underlying inflammation. MIF also has been reported to be elevated in such diverse autoimmune diseases as atopic dermatitis [45], psoriasis [46], sarcoidosis, Behçet's disease and the rare Vogt-Koyanagi-Harada's disease, especially in patients with uveitis [47]. The determination of urine MIF, as mentioned above, also may have diagnostic value in autoimmunity. Urine MIF may serve as a useful biomarker in diagnosing renal involvement in children with SLE [48].

The importance of MIF in lung diseases has been highlighted in different studies. Rossi et al. discovered that the MIF level in the bronchoalveolar lavage fluid of asthma patients is much higher than in patients with other inflammatory pulmonary diseases [18]. High serum levels of MIF also were observed in asthmatic patients [49]. A study by Bargagly et al. reported for the first time high MIF concentrations in lung tissue of patients with idiopathic pulmonary fibrosis. This finding is interesting because from a pathologic perspective this disease does not exhibit strong inflammatory features [50].

## 4. MIF in cancer

Cancer is characterized by six pathologic "hallmarks": self-sufficient proliferation, insensitivity to anti-proliferative signals, evasion of apoptosis, the potential for unlimited replication, the maintenance of angiogenesis, and, for malignancy, tissue invasion and metastasis [51]. Furthermore, it has been suggested from epidemiological studies that patients suffering from chronic inflammatory diseases have an increased risk in developing cancer. It is estimated that approximately 15% of cancer incidence worldwide is associated with microbial infection [52]. As an example, chronic infections with hepatitis B and C virus account for >80% of hepatocellular carcinoma cases, and infection with the gram-negative bacterium *Helicobacter pylori* is associated with an increased risk of gastric adenocarcinoma [53, 54]. With respect to the role of inflammatory signals in promoting the development of cancer, there is now emerging evidence for an important relationship between MIF expression, oncogenesis and tumor progression [55].

The first links between MIF and cancer were provided by experimental studies in mice. The administration of a neutralizing anti-MIF antibody in an animal model of B cell lymphoma inhibited tumor growth and angiogenesis [56]. High MIF expression by melanoma cells also was found to mediate angiogenesis, tumor growth, and migration in cellular and mouse model studies [57]. At a mechanistic level, MIF induces sustained ERK1/2 kinase activation,

which is notable because in most physiologic contexts ERK1/2 phosphorylation is transient. Thus, MIF produced by the tumor or by infiltrating inflammatory cells mimics the action of oncogenic RAS and appears to have the capability of replacing the requirement for RAS in sustaining ERK1/2 kinase activation. MIF also inhibits p53 activity and suppresses the transcriptional activity of p21, cyclin G1, and Mdm2 [58]. Although the p53 tumor suppressor is mutated in over 30% of human cancers, it has been noted that in many cancers, there are functional antagonists of p53 that are expressed that serve to bypass p53 inactivation. Accordingly, MIF may provide critical overriding signals that allow DNA replication to proceed despite damaging mutations that would otherwise be removed by p53-dependent apoptosis. Once *mif*-KO mice were developed, it was found that $mif^{-/-}$ cells do not show enhanced proliferation after oncogenic transformation, and the concurrent deletion of the *mif* and *p53* genes completely reversed the observed $mif^{-/-}$ phenotype [59].

One of the first clinical studies that examined MIF expression in human malignancy was in prostate cancer patients, where high serum levels of MIF were observed [60]. This initial report has since been extended by studies that have proposed a role for MIF both in prostate cancer detection and as an indicator of disease progression [61-63].

A proteomic study of serum factors in patients with ovarian cancer also pointed to the utility of measuring MIF in this disease [64]. The same authors have recently established a novel multiplex assay for six serum biomarkers (leptin, prolactin, osteopontin, insulin-like growth factor II, CA-125, and MIF). This combination of biomarkers appears to shows high sensitivity (95.3%) and specificity (99.4%) for the detection of ovarian cancer [64, 65] and it holds promise for the early detection of recurrent tumor, which is exceedingly difficult to treat. Agarwal et al. also reported that higher serum levels of MIF occur in ovarian cancer patients [66], and there is evidence that MIF may correlate with the presence of ascites. There are also experimental data that in ovarian cancer patients, MIF can down-regulate NKG2D, which is necessary for NK cell toxicity toward tumor cells [67]. These data would support the targeting of MIF as a target in treatment of MIF-dependent cancers.

The possible involvement of MIF in breast cancer also has gained attention. Jesneck et al. screened breast cancer patients and controls for 98 different serum proteins and reported MIF to be a valuable biomarker for detecting breast pathology. However, circulating MIF levels did not distinguish between benign and malignant tumors, suggesting that in this instance the protein probably was more indicative of a host inflammatory effect rather than tumor invasion [68]. Verjans et al. have suggested on the basis of their studies that there is a dual role for MIF in breast cancer: intracellular MIF may be beneficial because it was abundantly expressed in non-invasive breast cancer cells but not in invasive cell lines. Extracellular MIF nevertheless may exert a pro-oncogenic role by promoting breast cancer cell-stromal interaction [69].

In tumors of the gastrointestinal tract, MIF was found to be highly secreted by esophageal squamous carcinoma cells. Tumor differentiation and a patient's lymph node status also were observed to correlate well with intracellular levels of MIF [70]. A role for MIF as a biomarker in diagnosing and monitoring gastric cancer, either as a single marker or in combination with CEA also is supported by several studies [71-73]. High levels of MIF occur in colorectal cancer patients [74] and according to one report, MIF is more specific and more sensitive than CEA in detecting colorectal cancer. In addition, MIF has been described as a potentially predictive biomarker in hepatocellular carcinoma, bladder cancer, and non-melanoma skin cancer [75-77].

Several actions of MIF may promote oncogenesis or tumor progression in different cancers, as described above. MIF induces sustained ERK1/2-activation, similar to oncogenic RAS,

and it antagonizes p53-mediated apoptosis. These signals converge to promote cell cycle progression and escape from DNA-damage mediated growth arrest. Finally, several recent reports have described MIF to activate HIF-1α under hypoxic conditions [78]; this serves to activate a pro-angiogenic transcriptional program that is necessary for tumor progression. MIF downregulates the NK cell receptor NKG2D, as mentioned above, thereby impairing NK cell cytoxicity toward tumor cells [67] and it upregulates the anti-angiogenic factor thrombospondin-1 [79]. Nevertheless, the precise molecular mechanisms by which MIF mediates tumorigenesis in particular tumor types remain to be more precisely elucidated.

## 5. MIF in metabolic diseases

One of the most serious emerging threats to global public health are the metabolic diseases that constitute obesity, glucose intolerance, type 2 diabetes, and atherosclerosis. Decreased insulin sensitivity is the underlying defect in the majority of type 2 diabetes patients, and it is considered to be an important pathological mechanism for the development of cardiovascular disease [80]. An age-related resistance to the action of insulin also is a cardinal feature of the metabolic syndrome [81]. Recent animal and clinical studies have established not only correlative but also causal links between insulin resistance and chronic inflammation, especially within adipose tissue [82, 83]. C-reactive protein (CRP), for instance, is a widely used serum marker of systemic inflammation, and it is both independently related to insulin insensitivity and predictive of type 2 diabetes progression [84]. When infiltrated with monocytes/macrophages, adipose tissue releases proinflammatory cytokines (e.g. interleukin-6), CRP and fibrinogen. These mediators contribute by various mechanisms to the development of cellular insensitivity to insulin and to the characteristic vasculopathy of atherosclerosis [83].

The role of MIF with respect to inflammatory cell recruitment and plaque progression in the vascular wall has been described [6, 85-87]. There is evidence from experimental murine studies that MIF contributes directly to the metabolic derangement of severe or chronic inflammation in a TNF-independent fashion [88], and that it mediates the development of insulin resistance in adipose tissue [89]. Accumulating evidence also suggests that MIF may be involved in the pathologic sequelae of obesity or the metabolic syndrome. Yabunaka et al. first described that circulating MIF may be elevated in serum of type II diabetes in a study of 158 patients and gender-matched controls [90]. These findings were subsequently confirmed in a study of the type II diabetes-prone American Pima Indians [91]. More recent epidemiological data continue to support a potential role of MIF in the development of insulin resistance in humans. A strong association between systemic concentrations of MIF and impaired glucose tolerance was reported by Herder et al.[92] in their examination of 1653 patients with type 2 diabetes (n=236), impaired glucose tolerance (n=242) and normoglycemic control subjects (n=244). Notably, an association also was demonstrated between high expression *MIF* alleles and an increased risk of type 2 diabetes ($p<0.001$). In an intervention study, Church et al. examined MIF plasma levels in 71 severely obese individuals, who participated in a dietary weight management program [93]. High circulating MIF levels correlated with β-cell dysfunction, and MIF levels decreased after weight reduction 14.4 kg over 8.5 months ($p<0.001$). Finally, a recently published animal study provided mechanistic data in support of a role for MIF in the development of insulin resistance and atherosclerosis by promoting adipose tissue inflammation. This work also highlighted MIF as a potential therapeutical target in metabolic and cardiovascular disorders [94].

## 6. *MIF* alleles as biomarker

There is a single *MIF* gene in the human genome (22q11.2) that is characterized by the presence of a microsatellite repeat (−794 CATT) within the 5′ promoter region [95]. This repeat unit is present in 5-8 copies and lies within a putative Pit-1 transcription factor binding site. Both gene reporter assays and clinical studies indicate that repeat number is associated with higher *MIF* expression [95, 96]. Repeat number or a single-nucleotide polymorphism (−173 G/C) that is in strong linkage with $CATT_7$ are associated with increased clinical severity of rheumatoid arthritis [95, 96]. Subsequent genetic epidemiology studies have extended these finding to additional autoimmune inflammatory conditions, leading to the overall interpretation that high expression *MIF* alleles are associated with an increased innate response. These studies include juvenile forms of autoimmune arthritis [96, 97], asthma [98, 99], ulcerative colitis [100], psoriasis [101], and systemic sclerosis [41].

Of importance, the *MIF* allelic structure shows significant population stratification, with increasing repeat number following human migration patterns and genomic diversification [102]. In sub-Saharan Africa, there is a high prevalence of the $CATT_5$ allele; this led to the hypothesis that this low expression allelic variant provides protection from the inflammatory complications of malaria, since this region has suffered historically from the greatest mortality from this infection [102]. Initial studies in a mouse model of malaria have supported the beneficial role of *mif* deletion in severe malarial anemia [103]. Such a protective effect recently has been verified in a clinical study of 643 Kenyan children at high risk for lethal malaria; those with low expression *MIF* alleles were less likely to develop severe anemia as a consequence of infection [104]. Thus, *MIF* alleles that confer protection against the lethal inflammatory complications of malaria in Africans also render Western populations less susceptible to autoimmune inflammation.

The important role of *MIF* alleles in the host response to infection has been affirmed by the recently published work of the multicenter GenIMS (Genetic and Inflammatory Markers of Sepsis) Study Group, which completed the largest clinical study of genetic determinants of septic shock that has been performed to date. Over 1700 patients with community acquired pneumonia, which is the leading cause of intensive care unit admissions for sepsis in the US, were followed prospectively for survival and 21 different polymorphisms in innate immune response genes analyzed. MIF alone among these candidate genes was found to influence 90 day survival, with high expression alleles conferring a significant (~50%) survival benefit (hazard ratio=0.64). This result was somewhat unexpected given the prevailing hypothesis that an excessive innate response and inflammatory tissue damage underlies the immunopathogenesis of septic shock [105]. On the other hand, it is concordant with the notion that a strong innate response is necessary for the clearance of at least some invasive pathogens. Whether MIF is a clinically beneficial or detrimental mediator therefore may vary with the nature of microbial pathogen or the inflammatory stimulus.

The potential role of the *MIF* allelic system in the development of cancer is also coming under scrutiny. In a first report examining prostate cancer, where the presence of inflammatory cells on biopsy portends a poor prognosis, patients with the high expression $CATT_7$ allele were found to have an almost 5-fold increased risk of cancer recurrence [106]. This study was additionally noteworthy in that the genotyping determinations were all performed by amplifying the minute quantities of genomic DNA present in stored patient plasma. There also has been reported a recently completed study in gastric cancer, where carriers of the high expression $CATT_7$ genotype were observed to have a higher risk of developing gastric malignancy [107].

## Conclusion

There is now a wealth of data indicating that MIF expression is an integral part of the host response to tissue invasion, and that MIF may be readily measured in plasma and other tissue fluids in different disease states. The precise interplay between MIF and other host factors with respect to pathogenesis and disease progression is an important area of inquiry, and this point is emphasized by the genetic investigations of *MIF* alleles, where it remains to be determined for particular diseases whether MIF's role is beneficial or detrimental. The determination of *MIF* alleles nevertheless may be useful in predicting clinical course within a particular disease and in potentially guiding patient care. As an example, in sub-Saharan Africa where severe malarial anemia is a significant clinical problem [108], therapy requires hospitalization and blood transfusion, which is costly and carries some risk. Determination of genetic susceptibility thus can be applied to encourage hospital admission and to conserve blood resources for those children at highest risk of severe malaria and lethal outcome. Similarly, *MIF* alleles can be used to better stratify patients with community-acquired pneumonia so that those who are at greatest risk for progression to sepsis, severe sepsis, and septic shock can be identified, hospitalized, and treated aggressively. In the realm of autoimmune inflammatory diseases, *MIF* genotyping also offers the possibility of identifying those individuals in whom MIF pathways are activated and at greater risk for end-organ damage, or in the case of certain cancers, tumor progression. Finally, in the context of drug development, *MIF* genotype information may allow for the selection of those patients in whom pharmacologic inhibition of MIF offers greatest therapeutic benefit, and it may be useful for optimizing clinical trial design by focusing on those patients most likely to benefit from the pharmacological targeting of MIF.

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## Abbreviations

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| **MIF** | macrophage migration inhibitory factor |
| **MIF** | human gene for macrophage migration inhibitory factor |
| **mif** | mouse gene for macrophage migration inhibitory factor |

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