Review

Oncology

Oncology 2008;75:127–133
DOI: 10.1159/000155223

Received: October 15, 2007
Accepted after revision: May 19, 2008
Published online: September 15, 2008

Role of MIF in Inflammation and Tumorigenesis

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Key Words
Angiogenesis · Autoimmune diseases · Inflammation · MIF · Tumor

Abstract
MIF has been described as a protein that plays an essential role in both innate and acquired immunity. Previous studies have demonstrated that MIF activates lymphocytes, granulocytes and monocytes/macrophages. Furthermore, MIF can counteract the physiological function of steroids, thus playing a role in immune system regulation. Further evidence for a role of MIF in immunity was obtained in mouse models of autoimmune disorders, where the inhibition of MIF resulted in a more benign disease progression. This observation made MIF an attractive therapeutic target for the treatment of these disorders. Moreover, MIF expression was found to be upregulated in a variety of different tumor cells, a finding that further attracted interest. This review provides an overview of the involvement of MIF in both autoimmune disorders and tumorigenesis and summarizes the molecular action of MIF in this context.

Introduction

Macrophage migration inhibitory factor (MIF) was first described in 1966 as a molecule that inhibits the migration of macrophages [1, 2], thus giving rise to its name. Much research has been conducted on MIF since its discovery and it has been revealed that it primarily acts as a proinflammatory protein [3]. Furthermore, it has been shown that MIF not only acts on macrophages, but it is also produced by these cells in response to endotoxins, exotoxins and cytokines such as TNFα and interferon-γ [4]. In addition, it has been demonstrated that MIF-neutralizing antibodies protect mice against septic shock [5]. Subsequently, investigators demonstrated that MIF deficiency confers protection against lipopolysaccharide (LPS)-induced shock [6]. Antibodies directed against MIF are also capable of preventing T-cell activation. Recently, al-Abed et al. [5] provided evidence indicating inhibition of the immunological activity of MIF in a mouse model of septic shock. In this case, survival was significantly increased in mice treated with the tautomerase inhibitor ISO-1.

In addition to the previously described effects of MIF on innate immunity, its involvement in adaptive immune responses has also been proven. In 1996, investigators demonstrated that antibodies directed against MIF inhibit a delayed-type IV immune response. In vivo, T-cell activation and antibody production is inhibited by MIF [7].

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Molecular Basis of the Action Mechanism and Distribution of MIF within Various Cell Types

Structural analysis revealed that MIF is a molecule comprised of 115 amino acids with a molecular weight of 12.5 kDa [8]. The secondary structure of MIF consists of two antiparallel α-helices and six β-pleated sheets that are highly similar to MHC molecules [9]. In the active form of MIF, three monomers align in order to form a homotrimeric molecule that has a strong homology with the enzyme D-dopachrome-tautomerase [10]. Therefore, it has been hypothesized that MIF also displays some enzymatic activity. Knowledge on the physiologic substrate of MIF and the importance of this enzymatic activity is scarce [11]. However, when an inhibitor of the enzyme D-dopachrome-tautomerase (ISO-1) was employed, both human and murine wild-type and mutant MIF activity decreased in a system involving both human and murine mononuclear cells [12].

Even though much is known about the effect of MIF on various immune cells, it has taken quite some time for scientists to understand the signal transduction pathway that operates in many immune cells in response to MIF activation, especially given that this activation requires an extracellular receptor.

Initially, it was thought that there may be an interaction between sarcolectin (a constituent of albumin) and MIF [13, 14]. Though there were no immediate experimental data to support the truth of this biological interaction, Kleemann et al. [15] provided proof that MIF is taken up by cells and binds to Jab-1, inhibiting the activation of the transcription factor AP-1.

Experimental work from Leng et al. [16] extended the knowledge regarding MIF signalling by characterizing CD74 as a potential MIF receptor. CD74 is a nonpolymorphic type II integral membrane protein, which was initially considered to function predominantly as an MHC class II chaperone [17]. Recently, CD74 was also found to play an additional role as an accessory signaling molecule. In macrophages, CD74 demonstrates high-affinity binding to MIF. MIF binds to the extracellular domain of CD74; this complex is required for MIF-mediated MAPK activation and cell proliferation [16]. Furthermore, CD 44, a transmembrane coreceptor, is required for MIF-induced ERK1 and ERK2 kinase phosphorylation. MIF binding was associated with serine phosphorylation of both CD74 and CD44 receptors [18]. The activation of both receptors is required for MIF protection from apoptosis.

In addition to this interaction with CD74 and CD44 receptors, MIF was ascribed a role as non-cognate ligand for CXCR4 and CXCR2 [19]. These receptors were identified as functional receptors. MIF competed with known cognate ligands for these receptors and elicited monocyte arrest in inflamed atherosclerotic arteries, involving an interaction between CDCR2 and CD74 to form a receptor complex. Consequently, rapid integrin activation and calcium influx was observed. MIF deficiency impaired monocyte adhesion to cell walls in a mouse model of atherosclerosis. The authors concluded that MIF displays chemokine-like functions and acts as a regulator of inflammatory cell recruitment.

After receptor binding, the intracellular signalling cascade is activated via the ERK-MAP kinase pathway, resulting in increased cell proliferation via cyclin D1 transcription and subsequent phosphorylation of the Rb gene [16]. For fast and transient activation of this cascade, there is another pathway that involves Jab-1/CSN5, a protein that serves as an intracellular binding partner of MIF. In addition, a Src tyrosine kinase plays an important role and further enhances cell cycle progression [20, 21].

Furthermore, it has been demonstrated that the action of MIF increases calcium ion stores. This action by MIF results in a further influx of calcium ions from the extracellular space and most likely interacts via a second messenger. However, thus far a second messenger has only been shown in cells of the testes [22].

Abundance of MIF in Different Tissues

When MIF was first described [1], investigators hypothesized that it is secreted by T lymphocytes and acts upon macrophages. However, following this discovery, scientists demonstrated that macrophages produce and secrete MIF [4]. Some years later, expression of MIF was described in granulocytes and B lymphocytes [4, 23], thus indicating that the majority of inflammatory cells express MIF and that MIF plays a pivotal role in host defense.

MIF located in the brain contains mRNA that is primarily found within the cell body whereas the protein itself is located in the axons, indicating that there is likely a transport mechanism in place. Glial cells contain a rather homogenous distribution of MIF mRNA and a significantly lower concentration of MIF compared to neurons [24]. Moreover, most epithelial cells seem to express and store MIF. Given that the epithelial cell lining provides a first mechanical barrier against pathogens, the

presence of MIF in these cells may indicate that MIF plays a role in the early innate host defense [25].

Interestingly, the MIF protein has also been detected in the pituitary gland, specifically within ACTH-producing cells [26]. Of note, MIF secretion occurs in a circadian rhythmic pattern, with a late morning peak that coincides with peak cortisol levels [27].

Given the above descriptions of MIF in these different tissues, it seems highly likely that MIF not only plays an important role in host defense within the immune system but also has other physiological functions that have not yet been well characterized.

MIF and Its Role in Inflammation

MIF was first described as a soluble factor in the supernatant of antigen-stimulated cells as a result of studies that sought to gain insight into type IV allergic reactions (delayed hypersensitivity) [1, 2]. As a consequence, MIF was found to be produced by macrophages located in the cellular infiltrate following tuberculin injection. Interestingly, when applying antibodies directed against MIF, there was a reduced allergic reaction and the cellular infiltrate decreased considerably compared to control. Because of these observations, investigators concluded that MIF has a proinflammatory effect on cells.

The notion of MIF as a proinflammatory protein was further evaluated using a mouse model of septic shock [28]. After applying LPS, a potent activator of the innate immune system, MIF secretion and production measured by mRNA and protein synthesis increased compared to controls. However, when adding recombinant MIF, these effects were counterregulated. Use of antisense MIF led to decreased MIF concentrations in treated macrophages while higher amounts of mitogen-activated protein kinase phosphatase and lower concentrations of cytokines such as TNFα were observed. This study thus demonstrated the proinflammatory potential of MIF and stressed the importance of an autocrine action of MIF to override steroid-induced MKP-1 and to inhibit cytokine production [29].

Increased MIF secretion in response to inflammatory stimuli could be detected in many other tissues, thus undermining the function of MIF within the immune system. Following these observations, knockout mice were generated by different groups in order to examine the possible effect of LPS on these animals with regard to the severity of sepsis. However, the data obtained were subject to controversy as different groups reported different results. Bozza et al. [6] reported a reduced mortality rate in these knockout mice in response to LPS when compared to the control group. In contrast, Honma et al. [30] were not able to detect a significant difference in survival between the knockout mice and the controls.

Bacher et al. [7] noted that MIF also influences the proliferation and activation of T cells. Interestingly, it was later demonstrated that MIF not only has a direct effect on macrophages but is also secreted by them. Moreover, MIF is released and its production is increased in response to TNF and interferon [4]. This leads to increased production of NO and TNFα in an autocrine fashion, thus enhancing the removal of bacteria from infected tissue [31]. MIF was also shown to reduce the rate of apoptosis in neutrophil granulocytes [29].

As mentioned previously, MIF secretion results in an increased production and release of proinflammatory cytokines such as TNFα, interleukins and IFNγ. In a series of experiments by Roger et al. [29], MIF was found to influence the Toll-like receptor 4 (TLR4) located on macrophages and monocytes. The ligand for this receptor is LPS and thus bacterial toxin. MIF knockout mice were reported to express only low levels of this receptor. This may contribute to the less pronounced effects of LPS and thus lethal outcomes in this group.

Finally, MIF has been shown to be influenced by steroid secretion. Steroids are known to exert anti-inflammatory effects both in vivo and in vitro. Paradoxically, Calandra et al. [32] demonstrated that MIF expression can be induced by glucocorticoid release. Several mechanisms have been suggested to explain this mode of action [30]. Upregulation of intracellular phospholipase A_2 is one potential mechanism of action. Furthermore, MIF counteracts steroid-induced induction of MAP kinase phosphatase [29].

Physiological concentrations of glucocorticoids increase MIF secretion from murine macrophages [32] and MIF secretion is closely regulated. At high anti-inflammatory concentrations of steroids, MIF secretion is inhibited. This circumstance coupled with the inability of MIF to override steroid action indicates that there is some kind of escape mechanism that prevents an overwhelming inflammatory reaction from taking place [33]. In addition, MIF may regulate the degree of immune and inflammatory responses. This in turn would render MIF a powerful target for therapeutic modification since silencing the systemic effects of MIF could result in an unopposed anti-inflammatory response. This is especially important in the case of autoimmune disorders.

Several groups have provided evidence of MIF upregulation in atopic dermatitis, asthma, psoriasis, colitis ulcerosa and rheumatic arthritis [32–37]. Becker et al. [34] demonstrated a correlation between MIF and disease activity in vasculitis. The potential of MIF inhibition to reduce immune response was shown in knockout mice afflicted with inflammatory bowel disease and sepsis [6, 35].

MIF and Tumorigenesis

Repp et al. [36] showed that MIF inhibits lysis of melanoma cells by natural killer cells. This finding provides evidence that MIF may influence immune reactions related to tumor growth. Abe et al. [37] observed an increase in cytotoxic T lymphocytes following MIF inhibition as a result of specific antibodies. Moreover, the number of apoptotic tumor cells increased following MIF inhibition. In case that these cytotoxic cells provide an efficient means of tumor defense, modulation by MIF may contribute to the proneoplastic activity of the cell. The work of several groups points to a correlation between MIF expression and cancer prognosis. Specifically, this correlation has been demonstrated for hepatocellular carcinomas, colon cancers and prostate cancers [38–40].

Obviously, MIF also exhibits proneoplastic activity [41]. In many tumor cells and pretumor states, increased MIF mRNA could be detected in prostate [42], colon [40] and hepatocellular cancers [43], adenocarcinomas of the lung [44], glioblastomas [45, 46] and melanomas [45], for example. Recent research has focused on the understanding of increased MIF expression in these tumors and currently it is commonly believed that MIF plays several different roles that are discussed in detail.

Interestingly, MIF seems to affect both routes of the adaptive immune system. These two routes, namely the Th1 and the Th2 pathways, show varying cytokine profiles and induce different reactions. Th1 cells mainly secrete IL-2, IL-12, IFNγ and TNFα, which stimulate neutrophils and macrophages. In addition, IFNγ is a potent macrophage activator via the induction of MCP-1. The Th2 pathway counteracts the action of Th1. Cytokines include IL-4, IL-5, IL-10 and IL-13, with IL-10 being a potent endogenous immunosuppressant [46].

MIF affects these pathways in many different ways. Importantly, MIF sustains macrophage viability since it was shown that macrophages lacking MIF are prone to apoptosis. The action of MIF therefore leads to a more sustained inflammatory reaction [47]. It has been hypothesized that tumor-associated macrophages are able to promote the malignant potential of tumor cells [48]. The ability of MIF to preserve macrophage viability may therefore lead to tumor progression and the development of metastases. MIF also has a direct effect on T lymphocytes. Bacher et al. [7] showed that mitogen- and antigen-induced activation of Th2 lymphocytes greatly depend upon autocrine MIF secretion. As mentioned before, Th2 lymphocytes suppress the immune system, thereby further enabling tumor growth and development. Evidence for a role of MIF in the suppression of Th1 lymphocytes is provided by Abe et al. [37]. They observed that MIF inhibited the action of cytotoxic T lymphocytes. Since they are essential in antitumor activity via cytolysis of tumor cells, increased MIF levels in tumor cells may lead to resistance to the immune system. Therefore, MIF seems to be an important modulator in the development of tumors.

In 1997, Onodera et al. [49] demonstrated that mononuclear and multinuclear cells infiltrate inflamed pseudosynovial tissue. They could also show that these cells stained positive for MIF. In vitro experiments revealed active secretion of MIF by macrophages in response to phagocytosis of particles. A role for MIF in autocrine activation was postulated. These results can be adapted to tumor-infiltrating macrophages. This might be a possible first step in tumorigenesis. Using autocrine and paracrine mechanisms, MIF might not also prolong survival of macrophages but also of mutated cells.

One reason for the proneoplastic effect of MIF is its ability to proliferate. This was demonstrated for in vitro recombinant MIF in fibroblasts, where growth-factor-induced stimulation of these cells resulted in increased MIF concentrations, activation of the ERK-MAP kinase pathway and subsequent increase in cell proliferation [50]. This was also shown in a colon cancer cell line where the addition of TGFβ resulted in increased MIF expression [51].

In a recent study by Meyer-Siegler et al. [52], MIF influenced cell viability and invasiveness. In prostate cancer cells, androgen-independent prostate cancer cells required MIF-activated signal transduction pathways for both growth and invasion, which was in contrast to androgen-dependent cells. They demonstrated that the MIF cell surface receptor CD74 was only detected in androgen-independent tumor cells. Treatments directed against either CD74 or MIF resulted in decreased cell proliferation, MIF secretion and invasion. Further evidence for a role of MIF was obtained by Rendon et al. [53] using siRNA technique in human lung adenocarcinoma and

subsequent MIF knockdown. This resulted in a >90% reduction in both cell invasiveness and cell migration, in parallel with a reduction of Rac1, a RhoGTPase member. Interestingly, adverse effects were observed when MIF overexpression was achieved. These data underline the importance of MIF in tumor progression since invasiveness is an essential feature of metastasis.

Another important fact to note is that MIF is capable of inducing angiogenesis. Investigators demonstrated that MIF enhances the differentiation of endothelial cells to blood vessels [54, 55]. Using MIF antibodies or antisense mRNA, it has been possible to detect significant inhibition of angiogenesis in tumor cells. Furthermore, there is evidence that MIF might modulate VEGF functioning. In glioblastoma cells, Bacher et al. [56] demonstrated that MIF expression increased in cases of hypoxia and hypoglycemia, both of which are considered classical activators of angiogenesis. Further building on this work, Hira et al. [39] provided evidence of an increase in MIF expression and angiogenesis following hypoxia in hepatocellular carcinomas. One could therefore deduce a direct effect of MIF on angiogenesis. However, further research is required. In 2006, Baugh et al. [57] further revealed a possible role of MIF under hypoxic conditions. They describe HIF-1α as a potent inducer of MIF expression in hypoxia. Interestingly, these data were complemented by the works of Welford et al. [58]. They described the importance of HIF-1α in preventing cell senescence in a fibroblast model. Using HIF-1α knockout mice, they were able to show that under aerobic conditions lack of HIF-1α resulted in accelerated cellular aging and decreased cell proliferation under hypoxic conditions. In addition, they portrayed MIF as a factor influencing HIF-1α in delaying senescence. Evidence of the importance of MIF in the interaction between HIF-1α and tumorigenesis is provided by Winner et al. [59]. MIF is necessary for binding and stabilization of HIF-1α by CSN5. After stabilization, HIF-1α leads to transcription of oncogenes and growth factors and also of MIF. The authors propose that the MIF-HIF-1α interaction leads to amplification of hypoxia-dependent transcription.

Another plausible mechanism for the proneoplastic effect of MIF could result from inhibition of p53 apoptosis. Initially, the interaction of MIF with p53 was shown by Hudson et al. [60] in 1999. They demonstrated that MIF treatment was able to overcome p53 activity and inhibited its transcriptional activity. Other groups provided further evidence for a role of MIF in influencing p53. Fingerle-Rowson et al. [61] used a MIF-knockout mouse model and examined mouse fibroblasts where they found p53-dependent growth alterations and an increase in transcriptional activity of p53. In addition, these fibroblasts were resistant to ras-mediated transformation. Interestingly, when p53 deletion occurred, the observed phenotype was reversed in vivo. Similar evidence was obtained by Petrenko et al. [62] who used MIF null fibroblasts and described a growth retardation which correlated with a decreased susceptibility to Ras-mediated transformation. E2F induction was reported as an important feature, resulting in either G1 arrest or induction of apoptosis in p53-positive cells.

Recently, further evidence of the effect of MIF on cell cycle regulation was gained by the groups of Nemajerova et al. [63] and Winner et al. [64]. This involved SCF, a multi-subunit complex composed of four polypeptides. It is part of the large group of E3 ubiquitin ligases. In brief, these enzymes covalently attach ubiquitin to substrate proteins, which in turn are recognized and degraded by the proteasome [65]. It was recently shown [63] that MIF plays a role in regulating the activity of SCF, a known cell cycle regulator. Loss of MIF seems to disconnect certain DNA damage checkpoints and SCF-dependent degradation of specific cell cycle regulators, leading to a genetically instable situation.

Another pathway involved is ERK activation and induction of COX-2, both being expressed in colon carcinoma [66], and there is evidence that blocking COX by nonsteroidal antiphlogistics is capable of reducing the likelihood of tumor development by inhibition of tautomerase activity of MIF [67].

In summary, MIF was initially described as a factor inhibiting macrophage migration [1]. Further studies demonstrated that MIF exerts a proinflammatory action. Thus far, the signalling pathways activated by MIF have not been entirely elucidated; however, an extracellular receptor for MIF was recently found, indicating MIF as a potential target for pharmaceutical action. In addition, there is a role for MIF in tumor proliferation and angiogenesis, thus rendering it an interesting oncological target.

The involvement of MIF in both tumorigenesis and autoimmune disorders makes it a potential target for pharmaceutical inhibition. Several small molecules inhibiting MIF action have been developed and are currently being tested in clinical trials [68, 69].

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