Macrophage Migration Inhibitory Factor in Cardiovascular Disease

Alma Zernecke, MD; Jürgen Bernhagen, PhD; Christian Weber, MD

Abstract—The highly conserved and archetypical yet atypical cytokine macrophage migration inhibitory factor (MIF) fulfills pleiotropic immune functions in many acute and chronic inflammatory diseases. Recent evidence has emerged from both expression and functional studies to implicate MIF in various aspects of cardiovascular disease. The present review is aimed at providing a synopsis of the involvement of MIF in the inflammatory pathogenesis of atherosclerosis and its consequences, namely unstable plaque formation, remodeling after arterial injury, aneurysm formation, myocardial infarction, or ischemia-reperfusion injury. In addition, other forms of myocardial dysfunction and inflammation and the role of MIF in angiogenesis are reviewed. The functional data are reconciled with recent progress in the identification of heptahelical (CXC chemokine) receptors for MIF, its prototypic role as their noncanonical ligand, and its signal transduction profile operative in atherogenic and inflammatory recruitment of mononuclear cells and in the oxidative damage and apoptosis of cardiomyocytes. Its unique features and functions clearly distinguish MIF from other cytokines implicated in atherogenesis and make it a prime target for achieving therapeutic regression of atherosclerosis. The potential of targeting or exploiting MIF for therapeutic strategies or as a diagnostic marker in the management of cardiovascular diseases or disorders is scrutinized. (Circulation. 2008;117:1594-1602.)

Key Words: atherosclerosis ■ cytokines ■ inflammation ■ myocardium ■ remodeling

Atherosclerosis with its clinical manifestations myocardial infarction, stroke, and peripheral artery disease is close to becoming the leading cause of death worldwide. An impressive body of evidence supports the concept that atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by an influx of immunocompetent mononuclear cells1–3 that determine the delicately adjusted 2-edged immune balance and proinflammatory or antiinflammatory response.

The atherogenic recruitment of leukocytes is controlled by functionally specialized chemokines.2,4 Secreted into the soluble phase, chemokines were first discovered to mediate directed chemotaxis of leukocytic cell types. Subsequently, chemokines have been recognized as being transported and presented on the endothelial surface, where they are instrumental in triggering the integrin-mediated arrest of rolling leukocytes.5,6 In the context of atherosclerosis, this arrest function has been best established for the platelet-derived chemokine CCL5, the CXC chemokines, and the CXCR2 ligands CXCL1 and CXCL8.4

MIF is an evolutionarily ancient and highly conserved cytokine.7,8 From a historical perspective, MIF was originally described as a soluble factor expressed by T cells in delayed-type hypersensitivity responses exerting inhibitory effects on macrophage migration9 and may thereby represent the first known member of the cytokine family. Recently, MIF has been acknowledged to play pleiotropic roles in acute and chronic inflammatory diseases such as septic shock, rheumatoid arthritis, and colitis.4,10–12 Moreover, MIF has emerged as a key player in cardiovascular disease.13–15 As a molecule that is detectable in the circulation and at sites of inflammation, MIF might be an indicator of disease severity. In addition, MIF is unique among proinflammatory cytokines in that it is inducible by glucocorticoids (the Table), a mechanism that might be implicated in an acceleration of atherosclerosis associated with many diseases requiring glucocorticoid therapy.

Here, we discuss the novel receptor signaling routes of MIF and its functional role as a culprit and risk marker in vascular and myocardial processes and as a potential regulator of angiogenesis. We propose that MIF belongs to the group of “chemokine-like function” chemokines or “microchemokines.” This includes chemotactic polypeptides such as the β-defensins, which cannot be classified into known chemokine subfamilies but share structural or functional features and can signal through chemokine receptors.16,17

MIF in Primary Atherosclerosis

Hypercholesterolemia as the best documented risk factor contributing to atherogenesis instigates early endothelial ac-
**Table. Unique Features and Cardiovascular Effects of MIF**

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oxLDL indicates oxidized LDL; ATII, angiotensin II; ECs, endothelial cells; TNF-α, tumor necrosis factor-α; ICAM-1, intracellular adhesion molecule-1; PDGF, platelet-derived growth factor; AAA, abdominal aortic aneurysm; and LPS, lipopolysaccharide.

tivation or dysfunction accompanied by the expression of adhesion molecules and chemokines and thereby leads to early subintimal infiltration with mononuclear cells, the first morphological sign of inflammation in the arteries.2,18,19

Associated with the progression and severity of atherosclerotic disease, the expression of MIF has been shown to correlate with increased intima-media thickening and lipid deposition in the aorta of mice, in advanced human carotid artery plaques, and in rabbits fed an atherogenic diet.14,20–22 Moreover, elevations in systemic MIF concentrations have been shown to precede the onset of type 2 diabetes, which might be relevant in light of the fact that atherosclerotic vascular disease is more prevalent in diabetic patients than nondiabetic subjects.23 Different proatherogenic factors such as oxidized low-density lipoprotein (LDL), CD40 ligand, or angiotensin II have been shown to induce the expression of MIF in endothelial cells, smooth muscle cells (SMCs), mononuclear cells, and macrophages during the development of atherosclerotic lesions in humans, rabbits, and mice.14,15,22

As a cytokine, MIF is unique in that it is inducible by glucocorticoids and overrides or reverses glucocorticoid effects.24 This is particularly notable in light of recent findings that the inhibition of enzymatic generation of cortisol from inactive cortisone, lowering intracellular glucocorticoid levels, resulted in a dramatic reduction in atherosclerosis.25 This was associated with an increase in proinflammatory chemokines, suggesting an induction of local cytokines, ie, putatively MIF, by glucocorticoids to explain the proatherogenic effects and to provide a mechanistic link between glucocorticoids and atheroma formation.11

Evidence for the in vivo relevance of MIF in disease progression was obtained by antibody inhibition studies and animal models using the genetic deletion of MIF. In apolipoprotein E–deficient (Apo-e−/−) mice fed a normal chow, the neutralization of MIF impaired the atherogenic recruitment of macrophages and the aortic expression of inflammatory mediators, eg, matrix metalloproteinase (MMP)-2, CD40 ligand, and tumor necrosis factor, and was associated with a slight reduction in the development of atherosclerotic plaque area in the aorta.26 Similarly, the genetic deletion of MIF in LDL receptor–deficient (Ldlr−/−) mice retarded diet-induced atherogenesis, manifest as a decrease in intimal thickening and lipid deposition in the aorta.27 More recently, MIF deficiency in bone marrow cells after reconstitution in chimeric Apo-e−/− mice was found to markedly impair the recruitment of monocytes to lesion-prone areas, and the treatment with a blocking MIF antibody notably resulted in a regression of established atherosclerotic lesions with reduced macrophage and T-cell content in the aortic root.13 In these studies, strong evidence has been put forward that a major proportion of proatherogenic MIF effects are due to a direct enhancement of macrophage and T-cell recruitment (Figure 1).

**Chemokine-Like Functions of MIF in Inflammatory Cell Recruitment**

The superfamily of chemokines governs leukocyte trafficking and deployment during immune and inflammatory reactions by signaling through corresponding G-protein–coupled re-
The recent discovery that the host cytokine MIF fulfills chemokine-like functions in inflammatory cell recruitment indicates that alarmins such as the defensins and host autoantigens released from damaged cells, induce chemotactic cell migration through binding to CCR6, whereas the cognate ligand CCL20 shares antimicrobial properties because of a similar surface topology of positively charged residues. Autoantigenic aminoacyl-tRNA synthetases and their fragments, released from damaged cells, induce chemotactic cell migration through binding to CCR5 (HisRS) and CCR3 (AsnRS), and fragments of TyrRS mediate proangiogenic activity by direct binding to CXCR1 through a CXCL8-like N-terminal ELR motif.

The discovery that the host cytokine MIF fulfills chemokine-like functions in inflammatory cell recruitment indicates that alarmins such as the defensins and host autoantigens released from dying cells or after pathogen challenge exploit the chemokine receptor system to further encompass the recruitment of mononuclear cells and neutrophils. The receptor mechanism(s) underlying its cytokine activities have been elusive for decades.

Insight into the mechanisms involved in monocyte recruitment by MIF was first gathered in vitro. Adhesion assays revealed that short-term incubation of aortic endothelial cells with MIF triggered the arrest of monocytes under flow conditions. Moreover, monocyte arrest of endothelial cells induced by oxidized LDL was mediated by endogenously produced endothelial MIF. This observation supported a model whereby MIF directly affects endothelium-monocyte interactions by a novel mechanism that resembles the function of immobilized chemokines. The molecular machinery that underlies these effects has only recently been better understood as a consequence of the identification of the chemokine receptors CXCR2 and CXCR4 as functional receptors for MIF. MIF can trigger a calcium influx through CXCR2 or CXCR4, induces a rapid activation of integrins, and can subsequently mediate the G-protein-dependent arrest and the chemotaxis of monocytes and T cells (Figures 2 and 3). Thus, the earlier inhibition of macrophage migration giving rise to the original designation of MIF may possibly correspond to an inhibition of random migration while favoring directed migration.

Although roles for both MIF and CXCR2 in the initiation and progression of atherosclerosis have been established in various models, we only recently have been able to show that blocking Mif (as a dual Cxcr2/Cxcr4 agonist), but not the neutralization of the canonical ligands of Cxcr2, ie, KC, led to a regression of preexisting atherosclerotic plaques in Apoe-/- mice and that both macrophage content and T-cell content are reduced, consistent with a more stable plaque phenotype. Importantly, the function of MIF as a T-cell agonist and the notion that blockade of MIF impaired CXCR4-supported T-cell recruitment also may be important for driving lesion development. Thus, MIF is involved in leukocyte recruitment in a more universal sense than hitherto appreciated, and a picture evolves as to whether MIF has an...
efficacy similar to specialist cognate ligand chemokines but, in contrast to these ligands CXCL8 and CXCL12, which act in a more cell-restricted manner, promotes the recruitment of both monocytes and T cells by interacting with CXCR2 and CXCR4, respectively. Moreover, through CXCR2, the chemotactic activity of MIF extends to neutrophils.13 Besides these chemokine-like functions of MIF, a part of the effect on macrophage recruitment may be due to an enhancement of CCL2 release and induction of other inflammatory mediators such as adhesion molecules and tumor necrosis factor42 aggravating and sustaining the mononuclear cell influx. In fact, MIF might act sequentially by first directly promoting monocyte arrest through the CXCR axis and then promoting monocyte transmigration through the intermediate production of CCL2 (Figure 1). By analogy to complement-based defense mechanisms, MIF thus has been proposed to represent an archaic “master regulator” or preformed “source code” for leukocyte arrest and chemotaxis.13 This term also may be appreciated and justified from the plethora and multitude of unique features and cardiovascular effects of MIF (the Table), which make it stand out from many other cytokines and may indeed indicate a proximal role in the hierarchy of cytokines.

Hence, we propose that the emergence of host proteins with structural relationships to bona fide chemokines and with direct evidence for binding and signaling through chemokine receptors warrants an amendment of the current chemokine classification scheme43 by the addition of CC chemokine-like and CXC chemokine-like ligands (J.B. and C.W., unpublished data, 2007).

Figure 2. Signaling via a functional MIF receptor complex. MIF can be induced by glucocorticoids overriding their function by regulating cytokine production and, after its endocytosis, can interact with intracellular proteins, namely JAB-1, thereby downregulating MAPK signals and modulating cellular redox homeostasis. On the other hand, extracellular MIF has been found to bind to the cell surface protein CD74 (invariant chain Ii). CD74 lacks a signal-transducing intracellular domain but interacts with the proteoglycan CD44 and mediates signaling via CD44 to induce activation of Src-family kinase and MAPK/extracellular signal-regulated kinase (ERK), to activate the PI3K/Akt pathway, or to initiate p53-dependent inhibition of apoptosis. MIF also can bind and signal through G protein–coupled chemokine receptors (CXCR2 and CXCR4) alone. Complex formation of CXCR2 with CD74, enabling accessory binding, appears to facilitate GPCR activation and formation of a GPCR-RTK-like signaling complex to trigger calcium influx and rapid integrin activation.

Figure 3. Effects of MIF in myocardial pathology. In the context of ischemia-reperfusion, hypoxia, reactive oxygen species (ROS), and endotoxins (eg, lipopolysaccharide [LPS]) in sepsis can induce the secretion of MIF from cardiomyocytes through a protein kinase C (PKC)–dependent mechanism and can result in extracellular signal-regulated kinase (ERK) activation, which may contribute to cardiomyocyte apoptosis. Expressed by surviving cardiomyocytes or by endothelial progenitor cells (eg, eEPCs) used for therapeutic injection, MIF may promote angiogenesis via its receptors CXCR2 and CXCR4, requiring MAPK and PI3K activation.

The Functional MIF Receptor Complex for Atherogenesis

Notably, the atherogenic or inflammatory monocyte recruitment induced by MIF not only relied on CXCR2 binding but also involved the MIF-binding protein CD74, which colocalized with CXCR2 in the cell membrane of macrophages and after ectopic expression in B cells. The interaction of CXCR2 and CD74 strongly indicates that MIF signals via a functional CXCR/CXCR74 complex, which may explain downstream events such as calcium influx, mitogen-activated protein kinase (MAPK) activation, or Gαi-dependent integrin activation (Figure 2). Although CD74 lacks a signal-transducing intracellular domain, MIF-induced signaling via CD74 has been found to involve the proteoglycan CD44 and Src kinases.44 It is conceivable that CD74, CD44, and Src could form a functional receptor tyrosine kinase (RTK)–like complex. Although MIF can bind to CXCR2 alone, as evident in cells devoid of CD74, accessory binding to CD7445 may facilitate G protein-coupled receptor (GPCR) activation and formation of a signaling complex with Src kinases, resembling the use of CD44 as an auxiliary receptor by CCL5.46 Interestingly, phosphatidylinositol 3-kinase (PI3K) inhibitors potently interfered with MIF-induced chemotaxis of monocytes. This could indicate that engagement of the RTK/GPCR-like MIF receptor signaling complex may lead to the upstream recruitment of PI3K and Akt, consistent with data showing a promotion of cell survival via activation of the PI3K/Akt pathway by MIF in fibroblasts or tumor cells.47 The notion that CD74 contributes to MIF-independent CXCR2 functions in atherogenic recruitment13 is underscored by its preferential expression on mononuclear cells relevant to atherosclerosis45 and by a moderate recruitment activity of MIF in neutrophils lacking CD74 but also may reflect a more general involvement of CD74 in chemokine receptor signaling.

In addition, MIF taken up by endocytosis has been found to interact directly with intracellular proteins such as jun-c activation domain-binding protein-1 (JAB-1), which colocalizes with MIF in atheroma. Intracellular MIF can negatively regulate MAPK signaling or can modulate cell functions by regulating cellular redox homeostasis through JAB-1 as a possible feedback loop.11,14,48 As the only known cytokine,
MIF has been described to downregulate basic and phosphor-
ylated p53 expression (Figure 2), resulting in inhibition of
apoptosis and prolonged survival of macrophages in particu-
lar after cellular stress.49,50 This may contribute to increased
foam cell formation19 and may partially explain the athero-
protective effect of blocking MIF because p53 deficiency
promotes primary atherosclerosis.51

**MIF During Arterial Remodeling After Injury**

The mechanical injury of stenotic atherosclerotic lesions by
percutaneous intervention such as balloon angioplasty or
stenting as a therapeutic measure in the treatment of athero-
sclerotic and narrowed arteries induces the development of
neointimal hyperplasia in virtually all patients.52,53 In contrast
to primary atherosclerosis, the acute injury of the vessel wall
comprises the acute endothelial denudation and platelet ad-
hesion, as well as a massive apoptosis of SMCs in the medial
vessel wall. The accumulation of phenotypically unique
SMCs within the intimal layer in response to injury functions
to restore the integrity of the arterial vessel wall but subse-
quently leads to the progressive narrowing of the ves-
sel.52,54,55 A study of balloon injury in cholesterol-fed rabbits
showed that the early intimal monocyte infiltration precedes
the accumulation of SMCs and suggested that monocyte
recruitment subsequently triggers a more sustained and
chronic inflammatory response, possibly by releasing cyto-
kines and growth factors, leading to the ongoing monocyte
influx and SMC accumulation during neointimal growth.56

The role of MIF in neointimal lesion formation was first
studied after arterial air desiccation in Ldlr−/− mice in which
antibody blockade of MIF inhibited neointimal formation and
was associated with reduced inflammation and cellular pro-
iferation but increased apoptosis.57 Furthermore, the contribu-
tion of MIF to neointimal hyperplasia was analyzed after
wire injury of carotid arteries in Apoe−/− mice.15 MIF expres-
sion was upregulated in SMCs early after endothelial denu-
dation but was found predominantly in endothelial cells and
macrophage-derived foam cells at later stages. The neutral-
ization of MIF after injury led to a marked reduction in
neointimal macrophage content and inhibited their conver-
sion into foam cells. Conversely, the content of SMCs and
collagen in the neointima was increased.15 Although only a
slight reduction in neointimal area was observed, these
changes reflect a remarkable shift in the cellular composition
of the neointima toward a more stable plaque phenotype.

**MIF in Disease Progression and
Plaque Stability**

The impact of MIF in the regulation of SMC migration was
investigated more closely in vitro and demonstrated a bipha-
sic effect of MIF. Although short-term incubation with MIF
enhanced the platelet-derived growth factor-BB–induced vas-
cular SMC migration, long-term incubation with MIF de-
creased platelet-derived growth factor-BB–induced migra-
tion.58 Because platelet-derived growth factor-BB, together
with MIF, is present in vascular lesions, an impaired SMC
migration might contribute to plaque destabilization.58 In
addition, the proliferation of vascular cells also is influenced
by MIF27,58 and might contribute to the increase in plaque
cellularity and continuous growth. In this regard, it is inter-
esting to note that CXCR4, which has been implicated in
neointimal hyperplasia and the neointimal recruitment of
SMC progenitor cells,59 also can function as a receptor of
MIF. Thus, the MIF-induced proliferation of SMCs might
involve CXCR4 and play an important role in the progression
of neointimal formation and restenosis.

These data underscore the importance of MIF in arterial
macrophage accumulation and regulation of the lesional SMC
content, support the concept that MIF is strongly involved not
only in primary atherogenesis and plaque progression but also
after vascular injury, and imply a pathway for unstable lesion
formation involving MIF.

The genetic deletion of Mif also is associated with a
decrease in protease expression.27 Although MIF is known to
induce the expression of MMPs and cathepsins in vascular
SMCs, MIF also has been demonstrated to induce MMP-1
and MMP-9 in vulnerable plaques,27,60 indicating a role of
MIF in collagen degradation and weakening of the fibrous
cap and plaque destabilization.

Of note, polymorphisms in the MIF gene functionally
affecting the transcriptional activity of MIF have been corre-
lated with low disease severity in a cohort of rheumatoid
arthritis patients11,61 and might be relevant and useful for the
determination of disease progression and severity of
atherosclerosis.

**Aneurysm Formation**

In association with advanced atherosclerosis, abdominal aor-
tic aneurysms can occur as localized dilatations of the arterial
wall resulting from an extensive breakdown of structural
proteins caused by activated MMPs. These aortic aneurysms
can continuously expand and may eventually rupture, fre-
quently causing the death of the patient. Similar to advanced
plaques, the upregulated expression of MIF can be detected in
stable abdominal aortic aneurysm and is intensified further in
ruptured aneurysm. Notably, MIF serum levels are correlated
with initial aortic aneurysm size and annual aneurysm expa-
sion rates.62 Although MIF is expressed in endothelial cells,
SMCs, macrophages, and T cells, specific MMPs (MMP-1,
MMP-9, MMP-12) are upregulated and coexpressed with
MIF,53 implying an active role of MIF in the weakening of
vessel wall structures. A direct causal link needs to be
investigated by antibody inhibition and neutralization studies.

**MIF in Ischemia-Reperfusion and
Myocardial Infarction**

An upregulation of myocardial MIF expression also has been
observed in surviving cardiomyocytes and macrophages in a
rat model of acute myocardial ischemic injury.64 In the
pathogenesis of ischemia/reperfusion injury, reactive oxygen
species play an important role and can be generated from
cardiac myocytes and activate the transcription of several
genes (Figure 3). Both hypoxia and oxidative stress have been
demonstrated to induce the secretion of MIF from cardiomyo-
cytes through an atypical protein kinase C–dependent export
mechanism and to result in extracellular signal-regulated
kinase activation.65,66 Increased serum concentrations of MIF
also can be detected in patients with acute myocardial
infarction. MIF may thus play a role in the pathogenesis of myocardial ischemia and contribute to macrophage accumulation in the infarcted region and to their proinflammatory role in myocyte damage during infarction.

MIF and Angiogenesis

Tissue repair after myocardial infarction relies heavily on neoangiogenesis of the infarcted area. Recent evidence supports a role for MIF as an angiogenic factor because it mediates migration and tube formation in matrigel assays and induces angiogenesis in matrigel plugs and the corneal bioassay (Figure 3). These effects required MAPK and PI3K activation.67 In addition, MIF can be detected in tumor-associated neovascularature.66,68

Conversely, antibody blockade of MIF has been found to suppress tumor growth in models of B-cell lymphoma and colon adenocarcinoma and to inhibit tumor-associated angiogenesis.69,70 Interestingly, MIF expression in non–small-cell lung cancer occurs in close association with angiogenic CXC chemokines and vessel density, and high levels correlate with the risk of recurrence after resection.70 Because both chemokine receptors CXCR2 and CXCR4 have been involved in proangiogenic effects in various models of postnatal angiogenesis, including postischemic adaption,71–73 their function as signaling receptors for MIF may provide the molecular mechanism of action for the contribution of MIF to angiogenesis.

These data may provide a rationale for using MIF in therapeutic neovascularization for collateral development in ischemic cardiovascular disease. Indeed, embryonic endothelial progenitor cells induce blood vessel growth and cardio-protection under conditions of severe acute and chronic ischemia in a mouse ischemia-reperfusion model and a rat hind-limb ischemia model and have been attributed to the expression of a broad range of proangiogenic and remodeling factors, most prominently MIF.74

MIF Contributes to Myocardial Dysfunction and Sepsis

The dramatic improvement in survival from lethal endotoxemia by inhibition of MIF with a neutralizing antibody has initially and convincingly implicated MIF as an important factor in potentiating severe sepsis.75 Myocardial dysfunction as a major consequence of septic shock strongly contributes to the high mortality rates of sepsis.70 Because both chemokine receptors CXCR2 and CXCR4 have been involved in proangiogenic effects in various models of postnatal angiogenesis, including postischemic adaption, their function as signaling receptors for MIF may provide the molecular mechanism of action for the contribution of MIF to angiogenesis.

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Toward Therapeutic Targeting

As a key regulator governing inflammatory recruitment and subsequent events, MIF is a very accessible target for therapeutic intervention in immune-mediated and inflammatory diseases such as atherosclerosis.11 Given that mice genetically deficient in MIF display a rather normal and benign phenotype (compared, for instance, with deletion of other CXCR2 ligands) when unchallenged and that MIF is present at more abundant and less sharply fluctuating levels (again compared with CXCR2 ligands such as KC), MIF may represent a suitable target to avoid major adverse effects. The development of protein-based “biological” therapeutics such as anti-cytokine antibodies and soluble cytokine receptors may also prove to be a highly feasible approach for therapeutic targeting in the case of MIF.11 The favorable efficacy of an antibody to extracellular MIF has been supported not only in an animal model of sepsis but also in chronic inflammatory diseases.12,75,83 Importantly, an MIF antibody has been reported to be among the first strategies successful in inducing the regression of already apparent and established atherosclerotic lesions,13 reducing both macrophage and T-cell content resulting from the function of MIF as a dual CXCR agonist, and converting the composition of complex plaques into a more stable phenotype.15 Alternatively, soluble forms of CD74 recently identified as a cell-surface binding site for MIF on immune cells may be explored for this purpose by analogy to tumor necrosis factor-α.

Notably, MIF features 2 evolutionarily conserved motifs that have otherwise been identified only in bacterial enzymes and catalyze isomerization/tautomeration and oxidoreductase activities in vitro.84–86 Whether this catalytic center, which includes an N-terminal proline residue at position 2, is required for cytokine function of MIF in vivo remains a matter of controversy11,87; however, the homotrimeric tertiary structure of MIF has been implicated in both the assembly of the tautomerase region and interactions with CD74.43 Moreover, small-molecule inhibitors interacting with the active tautomerase pocket of MIF, namely the N-terminus incorporating the proline residue, can inhibit its cytokine function.88 As reviewed,89 these inhibitors comprise derivatives of hydroxycinnamate, Schiff-based tryptophan analogs, or imino-
quinoine metabolites of acetaminophen and could either directly affect critical residues or invoke a conformational change in MIF that prevents receptor or substrate interactions. It is tempting to speculate that targeting the N-terminal catalytic pocket of MIF with small-molecule inhibitors also would interfere with motifs relevant for CXCR2 binding and signaling. With regard to the recruitment function of MIF, it is noteworthy that MIF displays an atypical ELR motif characteristic of CXCR2 ligands with adequately spaced D and R residues in adjacent loops. Likewise, this could apply to an MIF-like redox-active peptide (MIF[50–65]), which can adopt MIF-like structural features and mimic MIF signal transduction events. Alternatively, peptide motifs from this region may serve as an alternative template for the development of small-molecule inhibitors. This approach could combine the usual advantages of small-molecule inhibitors (eg, oral availability, low antigenicity, and affordable production costs) with a cytokine-specific activity profile.

The emergence of numerous chemokine receptor antagonists exhibiting effects on mononuclear cell recruitment extends the current evidence supporting this therapeutic strategy despite the apparent redundancy in the chemokine receptor system. Given that MIF is becoming increasingly recognized as a target for treating inflammatory and cardiovascular disease and myocardial damage (the Table) that is currently under intense investigation as a therapeutic target. In particular, the abundance of unique features and the effects of MIF, most notably the first cytokine, the blockade of which results in both regression and stabilization of atherosclerotic plaques, clearly make MIF stand out among other cytokines implicated in the pathogenesis of atherosclerosis and may explain why its potential as a therapeutic target should be prioritized. Careful analysis of the structure-function relationship of MIF and its receptors will provide valuable information for customized drug development that may be feasible, eg, for cyclic anti-MIF treatment schemes. Given the remarkable benefits of blocking MIF in achieving plaque regression and stability and recent clinical disappointments encountered in exploring other strategies toward this end, eg, acyl-coenzyme A cholesterol acyltransferase or cholesteryl ester transfer protein inhibition, this concept would be highly attractive as a long-anticipated antiinflammatory treatment of established and unstable atherosclerosis beyond the use of statins. In light of the challenging obstacles, however, meticulous clinical testing is mandatory to validate and translate promising experimental data from animal experiments.

**Note Added in Proof**

While this article was in press, an intriguing report was published that demonstrated that MIF released in the ischemic heart stimulates AMP-activated protein kinase and thereby protects the heart against ischemia-reperfusion injury.94

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**Disclosures**

None.

**References**


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