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The vascular biology of macrophage migration inhibitory factor (MIF)

Expression and effects in inflammation, atherogenesis and angiogenesis

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Summary

Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine with chemokine-like functions. MIF is a critical mediator of the host immune and inflammatory response. Dysregulated MIF expression has been demonstrated to contribute to various acute and chronic inflammatory conditions as well as cancer development. More recently, MIF has been identified as an important pro-atherogenic factor. Its blockade could even aid plaque regression in advanced atherosclerosis. Promotion of atherogenic leukocyte recruitment processes has been recognised as a major underlying mechanism of MIF in vascular pathology. However, MIF's role in vascular biology is not limited to immune cell recruitment as recent evidence also points to a role for this mediator in neo-angiogenesis / vasculogenesis by endothelial cell activation and endothelial progenitor cell recruitment. On the basis of introducing MIF's chemokine-like functions, the current article focusses on MIF's role in vascular biology and pathology.

Keywords

Chemokine, monocyte/macrophage, cardiovascular disease, atherosclerosis, (neo-)angiogenesis/vasculogenesis

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Introduction: chemokines and vascular biology

The processes governing vascular homeostasis, vascular repair after acute injury and vascular remodelling during chronic disease are controlled and driven by a plethora of factors. Among them chemokines play a pivotal role at all levels of regulation.

Chemokines are small chemoattractant cytokines which have a molecular weight of 8-12 kDa. Chemokines exert a broad variety of functions in physiology and pathophysiology. In the context of the current review article, we will focus on their role in leukocyte chemotaxis, extravasation, as well as augmentation and/or attenuation of angiogenesis (1-3). Based on the arrangement of four conserved cysteine residues, chemokines are divided into four families (CC, CXC, CX3C, and XC) (4). Numerous examples of key roles of chemokines in vascular function, atherogenesis and vascular repair exist. A joint role for several of these molecular players can easily be rationalised, if one considers that the different steps of leukocyte recruitment process, i.e. rolling, firm adhesion, and transmigration are controlled by functionally specialised chemokines, which act in a sequential and cooperative manner. However, in the context of this review, we can only refer to some excellent previous review articles covering the aspects of a balance between chemokine redundancy and cooperativity in both the maintenance of vascular homeostasis and vascular pathology (3, 5-8).

Chemokine structure and function may be modulated by di-, tetrameric or perhaps even higher-order interactions. These interactions are usually homomeric (for a comprehensive review please see [9]), but chemokine function can also be modulated by heteromerisation, e.g. between CC and CXC chemokines. This may serve to promote chemokine/receptor interactions. An example for the latter is the heterodimerisation between CXCL4/PF4 and CCL5/RANTES, which takes place in α-granules of human platelets deposited at the glycosaminoglycan surface of endothelial cells *in vivo*. *In vitro* and *in vivo* studies revealed a pathophysiological function of such chemokine heterodimers (10, 11). In fact, von Hundelshausen et al. demonstrated that heterodimerisation of CCL5 and CXCL4 enhances CCL5-mediated monocyte recruitment, while Koenen *et al.* additionally identified peptidic inhibitors specifically interrupting the CCL5/CXCL4 interface and inhibiting vascular lesion formation in atherosclerotic *Apoe*$^{-/-}$ mice (10, 11).

A subfamily of the CXC chemokine family is known as the ELR+ chemokines and is defined by a glutamic acid-leucine-arginine (ELR)-motif near the CXC sequence. In contrast to non-ELR chemokines (ELR– CXC chemokines), chemokines from the ELR+ subfamily are potent inducers of physiological and pathological angiogenesis. They play important roles in diseases like cancer, fibroproliferative disorders and chronic inflammation like atherosclerosis (12-14). A representative example for an ELR+ chemokine is CXCL8/interleukin (IL-8). Thus, besides being a potent neutrophil chemoattractant, CXCL8 also plays an important role in neovascularisation in human non-small cell lung cancer (15), human gastrointestinal cancers (16) and human ovarian and pros-

tate cancer (17), where the CXCL8-CXCR2 axis regulates tumour angiogenesis accompanied by correlative reduction or enhancement of tumour growth. Further evidence for CXCL8-mediated angiogenesis in diseased tissue was found in human coronary artery plaques, where CXCL8 has been shown to be overexpressed (18). This might point to CXCL8-mediated growth of intra-plaque vessels and plaque destabilisation (19).

As an example for a prominent CC chemokine, the CCL2/CCR2 ligand receptor axis is important in monocyte chemoattraction and transendothelial migration into areas of vascular inflammation. CCL2 expression has been shown in atherosclerotic lesions, likely exacerbating lesion progression through extensive monocyte attraction and also through triggering firm monocyte adhesion to the inflamed endothelium (20, 21). A deletion or attenuation of CCL2 expression in atherosclerotic mouse models resulted in decreased lesion formation (22, 23).

In addition to the four canonical chemokine classes, a group of molecules sharing functional similarities with chemokines has emerged as a fifth subclass. This class has been referred to as 'chemokine-like function' (CLF) chemokines, non-canonical chemokines, or micro-chemokines. By definition, the CLF family of chemokines encompasses certain inflammatory and immune proteins that exhibit chemokine-like functions such as chemotactic properties or leukocyte arrest-promoting effects but which neither formally carry the typical N-terminal cysteine motif of the classical chemokines nor the chemokine fold. Most members of this functional family have been found to act as non-canonical ligands for classical chemokine receptors. CLF chemokines thus further expand the degree of redundancy and promiscuity in chemokine/chemokine receptor interactions, with consequences for angiogenesis regulation, as discussed below.

Examples are a cleavage fragment of tyrosyl tRNA synthetase (TyrRS) which has been shown to act as a non-canonical CXCR1 ligand via the presence of an ELR-like motif (24). The N-terminal 'mini-TyrRS' domain has proangiogenic properties and induces neutrophil chemotaxis through interaction with CXCR1 but not CXCR2 (24, 25). Interestingly, the ELR motif is only exposed and available for interaction with CXCR1 in the cleaved fragment (26). Similarly, autoantigenic aminoacyl-RS, released under apoptotic conditions, have leukocyte recruitment properties by triggering CC receptors. Both histidyl-RS and its N-terminal fragment are chemoattractants for several CCR5-expressing immune cells. Asparaginyl-RS interacts with CCR3 (27). For these aminoacyl-RS, the presence of specific surface charge distributions has been suggested to mediate chemokine receptor usage. Furthermore, the human antimicrobial peptides β-defensin-1 and -2 were identified as non-cognate ligands for CCR6, mediating chemotaxis (28). Again, although the sequence similarity between the β-defensins and CCL20 is limited, it appears that a cluster of cationic amino acids and shared electrostatic charge patterns account for the overlap in chemotactic activities. Promiscuity and mimicry mechanisms not only can be found endogenously in the host, but there are several examples of parasite or viral chemokine mimicry, encompassing both mimicry of classical host chemokine structures and CLF-type mimicry mechanisms (29, 30). Most prominently, HIV-1 capsid protein gp120 interacts with host CXCR4 (and CCR5) to direct leukocyte infection (29, 31). The nuclear protein high-mobility-group binding protein 1 (HMGB1) has been shown to exert numerous extracellular inflammatory functions. HMGB1 signals through several receptors (32, 33) and most recently, heteromeric complex formation between HMGB1 and CXCL12 was identified to mediate HMGB1 chemokine activities through CXCR4 (34).

In this review, we will focus on macrophage migration inhibitory factor (MIF), one of the first cytokines to be discovered (35) and another recent addition to the CLF family of chemokines (30, 36). In the next chapters, we will briefly outline both the physiology and the pathophysiologic roles of MIF in inflammatory and vascular disease, including underlying mechanisms such as its non-cognate interactions with the chemokine receptors CXCR2 and CXCR4. With regard to MIF's mechanisms of action, we will solely focus on aspects relating to vascular biology and pathophysiology.

MIF: structure, mechanism of action, and role in inflammatory disease

MIF is an evolutionarily-conserved protein that is abundantly expressed in humans and non-primate mammals. In addition to its functions as cytokine/chemokine and angiogenic factor (see below), it has been suggested that MIF also has anti-oxidative intracellular effects. The MIF structure is unique among cytokines. MIF consists of 114 amino acids and has a molecular weight of 12.5 kDa. The three-dimensional structure of human MIF shows that MIF crystallises as a trimer of three identical subunits, but studies at more physiological concentrations imply that the monomer may have crucial functions *in vivo* as well. Despite its wide tissue distribution, the secretion of MIF is tightly regulated, with relevant triggers such as hypoxia/ischaemia or oxidised low-density lipoprotein (oxLDL) of particular importance for this review article. Moreover, MIF expression is strongly up-regulated in several disease conditions most importantly in vascular pathology and tumourigenesis (37-39).

CD74, the membrane-expressed form of invariant chain (Ii) and an MHC class II chaperone, was identified as the first MIF plasma membrane receptor (40). CD74 expression is typically restricted to class II-positive cells, but under inflammatory conditions as well as in several tumour cell types, CD74 can be up-regulated, even in the absence of class II expression. MIF binds to CD74 by high affinity interaction in the nanomolar range, but signalling additionally requires the recruitment of signalling-competent co-receptors such as CD44 or CXCR2 and CXCR4 (see below). CD74 alone mediates MIF binding, but MIF-induced MAPK signalling requires the coexpression of CD44. MIF signalling through CD74/CD44 also involves the serine phosphorylation of the cytoplasmic tails of CD74 and CD44 and the recruitment of a Src-type tyrosine kinase (41). An architectural similarity between the MIF monomer and the CXCL8 dimer instigated biochemical investigations to probe potential interactions between MIF and CXCR2.

Receptor binding studies then revealed that MIF engages in a non-cognate, high affinity interaction with CXCR2 (42). CXCR2 had been known to be promiscuous previously, as it also is the receptor for six other ELR+ CXC chemokines including CXCL8. This as well as numerous functional data then suggested that MIF belongs to the family of CLF chemokines. The signal transduction pathways triggered by MIF/CXCR2 have not been studied systematically, but initial evidence shows that MIF binding to CXCR2 leads to G_i coupling and can elicit calcium transients. A limited screen of other chemokine receptors as well as an observed chemotactic effects of MIF on T cells, which do not express CXCR2 and only low levels of CD74, unraveled yet another MIF/chemokine receptor interaction, i.e. that with CXCR4. MIF/CXCR4 interaction is less affine than that between MIF and CXCR2 but still in the nanomolar range. Further research into the receptors of MIF revealed that CD74 forms heteromeric complexes with either CXCR2 or CXCR4 (42, 43).

During inflammation (44), endothelial cells do not only get activated but also adjust their phenotypes to the inflammatory response (45). Activation of endothelial cells (ECs), however, contributes to both acute and chronic inflammatory diseases such as sepsis, inflammatory bowel disease, rheumatoid arthritis, inflammatory lung disease, and atherosclerosis (46). There is ample evidence now that MIF is a key mediator of all of these disease conditions (37, 38, 47-49). Thus, MIF has been proven to play a pivotal role in the pathogenesis of both acute and chronic inflammatory diseases. Two prominent examples are sepsis and rheumatoid arthritis.

First evidence implicating MIF in systemic infection and sepsis dates back two decades ago when pituitary-derived MIF was found to contribute to serum levels of MIF in the post-acute phase of endotoxaemia. Employing a mouse model of endotoxic shock, MIF was found to promote lethal endotoxaemia in mice (50). Indeed, several and diverse models of septic shock have demonstrated the crucial role of MIF in mediating sepsis (51-53).

Rheumatoid arthritis, a systemic chronic inflammatory disorder of the joints, is characterised by key pathological events including diapedesis of leukocytes and the active participation of cytokines such as tumour necrosis factor (TNF). MIF has been extensively described to play a role in rheumatoid arthritis by e.g. inducing the secretion of CCL2 and to promote TNF production to amplify leukocyte recruitment at yet another level (38, 54). Of note, polymorphisms in the *MIF* gene functionally enhancing the transcriptional activity of MIF have been linked to increased disease severity of rheumatoid arthritis and other inflammatory conditions (38, 55).

MIF in the vasculature

Vascular endothelial cells exhibit a profound heterogeneity and organ specificity in terms of their phenotype and protein expression patterns. Depending on the vessel or tissue they inhabit, ECs are either strictly continuous with tight junctions, e.g. to maintain the blood-brain barrier or discontinuous in the case of the liver to allow for maximal fluid exchange. On the other hand, ECs lining the glomerulus are strongly fenestrated to allow for optimal filtration results. In large arteries, an additional requirement to resist high pressure and shear flow is found. ECs express various molecules that have been described to be pivotal in the pathogenesis of numerous vascular diseases such as atherosclerosis and angiogenesis. Among these molecules are various adhesion molecules, such as vascular cell adhesion molecules (VCAMs), intercellular adhesion molecules (ICAMs), selectins, and junctional adhesion molecules (JAMs).

The expression levels of MIF in human ECs of both microvascular and large artery origin have been shown to be upregulated upon treatment with oxLDL (56) or thrombin (57) in a time- and dose-dependent manner, suggesting a role for MIF in the vasculature. MIF released upon oxLDL stimulation contributes to atherogenic leukocyte recruitment (56, 58) (►Figure 1). Moreover, exposing human ECs to hypoxia led to a release of substantial amounts of MIF that was found to participate in the recruitment and migration of endothelial progenitor cells (59). The expression of MIF in the vasculature extends beyond the endothelial layer as vascular smooth muscle cells (VSMCs) have also been shown to express low levels of MIF (56); moreover, MIF expression was also observed to be upregulated by oxLDL in VSMCs (60). Importantly, VSMCs do not only express MIF but also migrate towards exogenous MIF after 6 hours (h) of incubation (61) (►Figure 1).

MIF signalling in the vasculature has also been pursued. Subsequent to showing MIF-induced expression of ICAM-1 in ECs (62), Cheng et al. reported the expression of VCAM-1, E-selectin, ICAM-1 and CCL2 to be MIF-dependent. Indeed, TNF-induced leukocyte rolling and adhesion to MIF-depleted human umbilical vein endothelial cells (HUVECs) were impaired, an observation that was attributed to a reduction of p38 MAPK activation, resulting in reduced expression of chemokines and adhesion molecules (63). In addition, MIF was found to upregulate mononuclear cell adhesion molecules such as VCAM-1 and ICAM-1 in a Src-, nuclear factor-κB (NF-κB), and phosphatidylinositol-3-kinase (PI3K)-dependent manner (64). The above findings are in line with a previous report where oxLDL- and MIF-induced monocyte arrest on HAoEC was abrogated by anti-MIF neutralising antibody (58). Moreover, MIF blockade leads to reduced VSMC proliferation and neointimal thickening (65), while at later stages during the atherogenic process MIF contributes to plaque instability (58). Thus, it is not surprising that there is extensive literature on the functional role of vascular MIF in the pathogenesis of vascular disease like atherosclerosis or neointimal growth after vascular injury.

MIF in atherosclerosis

Inflammatory processes are key contributors to the pathogenesis of atherosclerosis (66). The proinflammatory chemokine-like cytokine MIF has been broadly implicated in atherogenesis (39) (►Figure 1). Expression of MIF in developing atherosclerotic plaques in humans was minimal in ECs and smooth muscle cells (SMCs) in non-lesion-associated areas but was upregulated in ECs, SMCs, macrophages and T cells upon atheroprogression suggesting a role for MIF in plaque instability (56, 67). Interestingly,

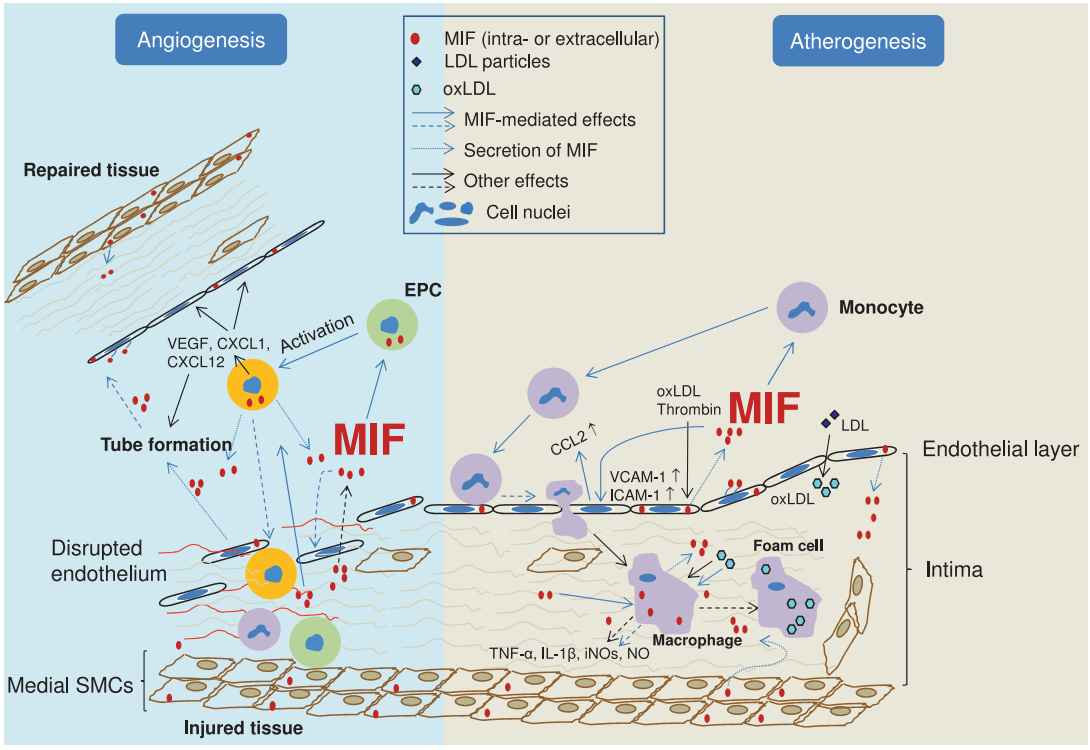

Figure 1: Expression and functional role of vascular MIF in angiogenesis and atherosclerosis. Left (angiogenesis): After tissue injury, MIF along with other chemokines such as CXCL12, CXCL1, and VEGF is released to activate and recruit EPCs and also monocytes to the site of injury where they are embedded into tube structures. Importantly, MIF drives tube formation and the formation of new vessels that follows. EPCs carry angiogenic factors ('cargo') themselves. Right (atherosclerosis): MIF expressed by ECs and macrophages in the atherosclerotic plaque is upregulated upon stimulation with inflammatory and atherogenic mediators such as oxLDL and thrombin. MIF induces the expression of chemokines (CCL2) and adhesion molecules (VCAM-1, ICAM-1) which regulates the recruitment and adhesion of monocytes to the surface of the endothelium. Alternatively, MIF may employ its chemokine receptors CXCR2 and CXCR4 (expressed on recruited monocytes and T cells, respectively; receptors not shown) in exerting its chemokine-like functions. After transmigration into the subendothelial space, monocytes subsequently differentiate into macrophages. MIF and other pro-atherogenic factors (latter not shown) stimulate these macrophages to secrete TNF-α, IL-1β, iNOS and NO, enhancing the inflammatory milieu in the lesion. Additionally, MIF potentiates foam cell formation by accelerating macrophage oxLDL uptake, thereby enhancing lesion formation. VSMCs express and also migrate towards MIF and this may contribute to plaque stability, although long term exposure to MIF has also been shown to inhibit PDGF-BB-induced VSMCs migration and MMP upregulation which points in the direction of plaque destabilisation by MIF (for references see text).

an interaction between MIF and CSN5/JAB1, a negative regulator of NF-κB which is a key transcription factor involved in the inflammatory and immune processes associated with atherosclerosis (68, 69), was revealed in human atherosclerotic lesions (56). As a negative regulator of CSN5, MIF might synergise with JAB1 in regulating NF-κB-driven inflammatory and immune signalling in atherosclerosis (70).

Atherosclerosis may be preceeded by vascular injury and MIF has been shown to regulate the biological response to the injured tissue. In a carotid artery injury model of atherosclerosis-susceptible mice, MIF was shown to potentiate neointimal thickening by promoting the accumulation of inflammatory cells in the neointima and the proliferation of medial and intimal cells (65). Indeed, neutralising MIF resulted in a reduction of neointimal macrophage content and an increase in SMCs and collagen type I content in the neointimal lesions in a model of vascular injury-induced accelerated lesion formation. This reduction in neointimal macrophage content was attributed to impaired monocyte recruitment as exogenous MIF increased the number of monocytes adhering to HAoECs, an effect that was dampened by neutralising MIF mAbs (58). The notion that MIF is critical in the development of atherosclerosis was corroborated by Mif gene-inactivation in *Ldlr*$^{-/-}$ mice. These mice showed impaired atherogenic diet-induced lesion initiation and progression when compared with corresponding wild-type mice. The ability of MIF to induce proliferation of SMCs which has previously been observed mainly by using mAb was confirmed by this genetic study (71). In a spontaneous atherogenic *Apoe*$^{-/-}$ mouse model, MIF was found to be elevated at the aortic wall and blocking aortic MIF with anti-MIF neutralising antibody led to a reduction in intimal macrophage content and inflammatory mediators (72). Notably, treatment with a blocking antibody that targets MIF even resulted in atherosclerotic plaque regression and a more stable plaque phenotype in diet-induced atherosclerotic *Apoe*$^{-/-}$ mice. This observation was reasserted by the finding that MIF mediates atherogenic monocyte and T cell recruitment *in vivo* by engaging its receptors CXCR2 and CXCR4, respectively (►Figure 1). Dual action of MIF through CXCR2 and CXCR4 also may explain why anti-MIF

blockade was more efficacious in the clinically highly relevant regression model than treatment with anti-CXCL1 or anti-CXCL12 (42). Indeed, a MIF N-loop-derived peptide that disrupts the interaction between MIF and CXCR2 blocked MIF-induced leukocyte adhesion in carotid arteries *in vivo* (73).

Taken together, data from several groups using either neutralising antibody or genetic deletion underpins the pathogenic role of MIF in promoting atherogenic changes in the arterial vessel wall. Importantly, the proatherogenic role of MIF was confirmed in epidemiologic studies where single nucleotide polymorphisms (SNPs) in the human *MIF* gene were identified as a risk factor for coronary heart disease, showing an association of a haplotype containing the rs755622C allele, which has been reported before to increase the susceptibility for various other proinflammatory conditions (74), and showing that the GG genotype of the MIF SNP rs1007888 was associated with myocardial infarction (MI) in Czech female patients (75). Moreover, Makino et al. showed that high plasma levels of MIF are associated with adverse long-term outcome in patients with stable coronary artery disease and impaired glucose tolerance or type 2 diabetes mellitus (76). Similarly, Müller et al. found that MIF expression is enhanced in acute coronary syndromes (ACS), that it is associated with various markers of the inflammatory response, that it correlates with the extent of cardiac necrosis marker release after percutaneous intervention and that it is increased in ACS patients with respective lesions (77).

Role of MIF in (neo-)angiogenesis / vasculogenesis

MIF's role in atherogenesis has been extensively studied (see above); however, its roles in the processes controlling physiologic and pathophysiologic angiogenesis are less well understood.

Angiogenesis is the growth of blood vessels from a pre-existing vasculature. It occurs throughout life and is an important component of different physiological and pathophysiological conditions such as wound healing and pregnancy (78). Regulation of angiogenesis is achieved by balancing angiogenic and angiostatic triggers. If not properly controlled, angiogenesis can promote to tumour growth, rheumatic arthritis, and retinopathies (78). The therapeutic value of angiogenesis has become of great interest. Inhibiting or decreasing angiogenesis possesses therapeutic potential in treating cancer and rheumatic arthritis, while stimulation of angiogenesis can be helpful in ischaemic heart disease, peripheral arterial disease, and wound healing responses by increasing reperfusion of the tissue. Moreover, vasculogenesis, a process formerly considered to be restricted to the *de novo* formation of vascular structures from mesenchymal angioblasts in early embryonic vascular development (79, 80), has now also been discussed to occur postnatally, where it is triggered by endothelial progenitor cells (EPCs[1]) (81-84), opening-up promising novel therapeutic avenues as well (85, 86).

Oxygen plays a crucial role in controlling angiogenesis. Hypoxic conditions stimulate vessel growth by activation of ECs (i.e. proliferation and migration). The cellular response to hypoxia is mediated via up-regulation of hypoxia-inducible transcription factors (HIFs), most prominently HIF-1α. HIFs upregulate the transcription of numerous genes, thereby affecting endothelial cell growth, SMC recruitment, and leukocyte attraction. HIF-1α is the best characterised inducer of the expression of vascular endothelial growth factor (VEGF), the major endothelial growth factor in angiogenesis and a key trigger of angiogenesis. Hypoxia-triggered VEGF production and the subsequent increase in oxygen supply following newly formed vessel growth reciprocally regulate each other to restore homeostasis following limited blood supply (86-88).

MIF was first implicated in angiogenesis some 14 years ago, when Chesney et al. found that MIF blockade by a neutralising antibody reduces tumour vascularisation and tumour growth in a murine model of B-cell lymphoma (89). Although several distinct mechanisms have been suggested to underlie MIF's potent pro-tumourigenic capacity, a role for MIF in tumour angiogenesis was confirmed in a model of colon adenocarcinoma formation, in which blockade of MIF led to reduced microvessel formation (90). Moreover, MIF expression is seen in non–small-cell lung cancer, a tumour entity in which MIF now has been firmly established as a crucial player (91-95). MIF expression occurs in association with angiogenic CXC chemokines and increased vessel density (70). As discussed above, MIF is a non-cognate ligand for CXCR2, the cognate receptor for angiogenic CXCL8, and MIF also promiscuously engages CXCR4, the cognate receptor for CXCL12. Although CXCL12 is an ELR– CXC chemokine, both CXCR2 and CXCR4 have been found involved in numerous pro-angiogenic effects in various models of postnatal angiogenesis, including post-ischaemic adaption (71–73), underscoring the notion that the chemokine receptors of MIF could be critical in mediating MIF-driven pro-angiogenic responses, although direct evidence from knockout mouse models is yet missing for this assumption (►Figure 1).

As for angiogenic factors such as VEGF, MIF expression was also identified to be regulated by HIF-1α activity, as demonstrated in lung tissue, ECs, hepatic stellate cells, and VSMCs (59, 96-98). A number of studies have since confirmed MIF's pro-angiogenic properties and explored the underlying molecular and cellular mechanisms. MIF mediates EC migration and tube formation in matrigel assays and induces angiogenesis in matrigel plugs and the cornea angiogenesis assay (►Figure 1). These effects rely on mitogen-activated protein kinase (MAPK) and PI3K signalling, activities known to be triggered by MIF (42, 99-101). Accordingly,

1 Endothelial progenitor cells (EPCs) were initially considered to represent a single entity of progenitor cells capable of supporting post-natal *de novo* blood vessel formation and have been assigned a crucial role in neo-angiogenesis. However, since their discovery in 1997 their phenotype has been refined and become more complex. In fact, EPCs exhibit different characteristics: (i) the so-called early outgrowth EPCs (EOCs) are derived from circulating CD34-positive mononuclear cells and additionally express CD45 and CD14; they exert enhanced adhesion proprieties but fail to proliferate in vitro; (ii) the so-called late outgrowth EPCs (LOCs), lack hematopoietic markers but have the ability to proliferate. Both subtypes respond to angiogenic stimuli, express CD31 and secrete angiogenic factors such as VEGF and angiogenic cytokines/chemokines by themselves (79-82).

MIF could be detected in the tumour-associated neovasculature and neointima following vascular injury in pro-atherogenic mouse models (58, 89, 99).

Tissue repair after MI heavily relies on neoangiogenesis of the infarcted area. Chemokines and their receptors play important roles during these 'repair' processes. Both exacerbating and pro-healing responses occur. For example, the genetic absence of CC chemokine receptor Ccr1 in a corresponding mouse model reduces functional impairment and structural remodelling after MI due to an abrogated early inflammatory recruitment of neutrophils and improved tissue healing including vessel regeneration (102). Interestingly, the CXCL12/MIF receptor CXCR4 was recently found to have a dual role in neo-angiogenesis after MI. CXCR4 was found to play a crucial role in endogenous remodelling processes after MI, contributing to inflammatory/progenitor cell recruitment and neovascularisation, whereas its deficiency limits infarct size and causes adaptation to hypoxic stress (103).

MIF has now been amply implicated as a protective factor in MI-ischaemia/reperfusion (I/R) injury. Although the protective mechanisms involved have been suggested to span from AMP kinase activation to promotion of anti-oxidative pathways (104-107), it is likely that MIF-driven angiogenic/vasculogenic processes are equally important. Indeed, MIF secreted from ECs by hypoxic stimulation has been identified to promote EPC chemotaxis in a CXCR4- (59) and CXCR2- (D. Simons and J. Bernhagen, unpublished observations) dependent manner (►Figure 1). This finding was intriguing, because previously CXCL12 was considered the main protagonist in driving EPC recruitment following hypoxic/ischaemic triggers (108, 109). However, these seemingly divergent findings may be readily reconciled if one considers the kinetics of chemokine production. Hypoxia-stimulated HUVECs and human aortic endothelial cells (HAoECs) did not secrete detectable CXCL12 levels within an early time window of 2 h, when MIF was predominantly secreted, peaking at 60 minutes (59). This nicely coincides with the findings by Ceradini et al. reporting that CXCL12 production from hypoxically challenged HUVECs and ischaemic tissue *in vivo* occurred in a time interval of 6-24 h and correlated subsequent EPC trafficking *in vivo* (109). Interestingly, a second MIF secretion peak was observed 8 h after the hypoxic trigger (59), indicating that within this intermediate time window MIF and CXCL12 may jointly act to drive EPC recruitment and neovascularisation (►Figure 1).

EPC recruitment and neovascularisation also represent important mechanisms driving the healing process of acute or chronic skin wounds. Accordingly, MIF was defined as a potential inducer of EPC mobilisation after flap operations. In flap patients, the number of circulating EPCs and serum levels of MIF but not CXCL12 serum levels was increased, especially in the patient group of free microvascular flaps. Also serum MIF and EPC levels correlated and MIF blockade, and to a lesser extent CXCL12 inhibition, partially reverted the chemotactic effect of patient serum on isolated human EPCs (110). The study also indicated that MIF-mediated EPC mobilisation is dependent on the degree of ischaemia (110).

As mentioned above, the neovascularisation potential of EPCs is in part due to the fact that these cells are carriers of numerous potent angiogenic/vasculogenic factors ('angiogenic cargo'). Prominent cargo factor are VEGF and thymosin-β4, but interestingly also MIF and other chemokines (111, 112). The differential usage of these factors was recently further refined by *in vivo* implantation experiments, indicating that the MIF/chemokine receptor axis has an important role in differentiation towards an endothelial and SMC phenotype (113). As murine embryonic EPCs were previously found to induce blood vessel growth and cardioprotection under conditions of severe acute and chronic ischaemia in a mouse I/R model and a rat hind-limb ischaemia model, the above study confirms the therapeutic neovascularisation potential of EPCs in combination with selected sets of angiogenic chemokines/factors, including MIF (112, 113).

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Conflicts of interest

None declared.

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