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Review

Evolving complexity of MIF signaling

Stanislovas S. Jankauskas[a], Dickson W.L. Wong[a], Richard Bucala[b], Sonja Djudjaj[a,1], Peter Boor[a,c,*,1]

[a] Institute of Pathology, RWTH Aachen University Hospital, Aachen, Germany
[b] Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA
[c] Department of Nephrology and Immunology, RWTH Aachen University Hospital, Aachen, Germany

A B S T R A C T

Macrophage migration inhibitory factor (MIF) is a cytokine expressed in various cell types, including hematopoietic, epithelial, endothelial, mesenchymal and neuronal cells. Altered MIF expression has been associated with a multitude of diseases ranging from inflammatory disorders like sepsis, lupus and rheumatoid arthritis to organ pathologies such as heart failure, myocardial infarction, acute kidney injury, organ fibrosis and a number of malignancies. The implication of MIF in these diseases was supported by numerous animal studies. MIF acts in an autocrine and paracrine manner via binding and activating the receptors CD74/CD44, CXCR2, CXCR4 and CXCR7. Upon receptor binding, several downstream signaling pathways were shown to be activated in vivo, including ERK1/2, AMPK and AKT. Expression of MIF receptors is not uniform in various cells, resulting in differential responses to MIF across various tissues and pathologies. Within cells, MIF can directly bind and interact with intracellular proteins, such as the constitutive photomorphogenic-9 (COP9) signalosome subunit 5 (CSN5), p53 or thioredoxin-interacting protein (TXNIP). D-dopachrome tautomerase (D-DT or MIF-2) was recognized to be a structural and functional homolog of MIF, which could exert overlapping effects, raising further the complexity of canonical MIF signaling pathways. Here, we provide an overview of the expression and regulation of MIF, D-DT and their receptors. We also discuss the downstream signaling pathways regulated by MIF/D-DT and their pathological roles in different tissue, particularly in the heart and the kidney.

1. Introduction

Macrophage migration inhibitory factor (MIF) was definitively cloned and described as a factor amplifying the systemic inflammatory response to endotoxin treatment in 1993 [1]. Since then, MIF has been shown to play a crucial role in mediating resistance to different pathogens [2–5] and driving various types of immune and autoimmune diseases [6,7]. MIF was also shown to be up-regulated in numerous types of malignancies and its expression correlates with the disease progression [8]. MIF exerts its biological functions in an autocrine and paracrine way [9–13] via the receptors CD74, CXCR2, CXCR4, and CXCR7 [14–16]. Upon MIF binding, CD74 does not induce signaling alone but requires the recruitment of CD44 or CXCR receptors [17]. There are several possible complexes formed between these receptors, including CD74/CD44 [17–19], CD74/CXCR2 [15], CD74/CXCR4 [20] and CD74/CXCR4/CXCR7 [16]. Up till now, it is not completely clear whether CD44 is also involved in the receptor complexes of CD74 with the CXCRs. Evidence for the induction of MIF signaling solely via CXCR7 was reported recently [21]. Tissue specific expression of MIF receptors and co-receptors (i.e. CD44) determine the tissue responsiveness to MIF. Recently, the vestigial enzyme D-dopachrome tautomerase (D-DT) was recognized as a structural and functional MIF homolog, bringing to life the concept of a “MIF cytokine family” [22,23].

In the first part of this review, we provide a general overview of the structure of MIF protein, regulation of *MIF* gene transcription in different cell types and summarize the published data on D-DT. In the second part, we give an overview of the MIF and D-DT receptors, their intracellular interacting partners and the downstream signaling pathways. In the third part, we summarize the data about tissue-specific effects of MIF and D-DT signaling by taking the heart and the kidney as two examples. The important roles of MIF in (auto)inflammatory and malignant diseases were summarized in a number of excellent review articles [24–27]. Here, we focus on the less well-understood and yet underappreciated roles of MIF signaling.

2. MIF and D-DT

2.1. MIF and D-DT protein structure

MIF is composed of 114 amino acids with a molecular weight of approximately 12.5 kDa [28]. MIF forms a homotrimer with a barrel-

* Corresponding author at: Institute of Pathology, RWTH Aachen University Hospital, Pauwelsstrasse 30, 52074 Aachen, Germany.
E-mail address: pboor@ukaachen.de (P. Boor).
[1] Authors contribute equally to the study.

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shaped structure and a solvent assessable channel in the middle [29]. MIF is highly conserved among vertebrates but is also found in arthropods, nematodes, and protozoans [30]. MIF executes the phenylpyruvate tautomerase activity that catalyzes the conversion of D-isomer of 2-carboxy-2,3-dihydroindole-5,6-quinone (D-dopachrome) to 5,6-dihydroxyindole-2-carboxylic acid (DHICA) [31]. A precursor of the D-dopachrome is a D-Tyrosine and this amino acid is not synthesized in vertebrates. Thus, the biological role of MIF enzymatic activity in vertebrates is still unclear and seems to be vestigial. The abolished tautomerase activity of MIF either by the imine formation or carbamylation of the N-terminal Proline within the active center didn't affect its signaling activity in mice [32].

Several post-transcriptional modifications of MIF were described [33]. Intracellular MIF was shown to undergo S-nitrosylation on Cystein-81 [34], cysteinylation of Cystein-60 [35] and phosphorylation of Serine-91 [35]. Modification of Cystein-60 and Serine-91 was shown to occur in the Ts hybridoma 31E9 cells in vitro and was suggested to modulate MIF's bioreactivity in these cells [35]. The S-nitrosylation of MIF was shown to occur in heart tissue in vivo after nitrite injection to the left ventricle [34]. Nitrite injection was cardio-protective against ischemia/reperfusion injury of the heart by itself, and this effect was amplified by the addition of recombinant MIF, but not mutated MIF with substitution of Cysteine-81 to Serine. This suggested S-nitrosylation of MIF as a potential intrinsic cardio-protective mechanism during ischemia/reperfusion and increased NO production. Interestingly, both recombinant and mutated MIF were cardio-protective also in the absence of exogenous nitrite, but to a lesser extent [34]. Extracellularly, MIF's Proline-2 is sensitive to oxidation by myeloperoxidase-derived oxidants, e.g. produced by activated neutrophils. This modification resulted in complete abrogation of MIF's tautomerase activity, but didn't affect MIF's capacity to prevent neutrophil apoptosis [32]. Proline-2 of MIF can be also covalently modified by dietary isothiocyanates, which were shown to affect the tertiary structure of MIF resulting in diminishing MIF activity, i.e. counteracting glucocorticoids action and AKT phosphorylation [36]. Some other post-translational modifications of MIF, such as S-glycosylation at several positions, are reviewed in more detail elsewhere [33]. The significance of such post-translational modifications in regulating MIF action *in vivo* for the most part remains to be established.

Most studies showed a cytoplasmic localization of MIF [37–39]. In the cytoplasm, MIF is stored in vesicle-like structures [40] and secreted in response to a number of stimuli including lipopolysaccharide (LPS) [1,41–44], tumor necrosis factor (TNF)-α [45,46], hypoxia [12,47], H_2O_2 [47], thrombin [9,48] and angiotensin II [49]. Most secreted proteins encode a 16- to 30- amino acid residue signal sequence which directs proteins from the endoplasmic reticulum with further translocation to the Golgi apparatus and to secretory vesicles [50]. This signal sequence is not found in MIF [51,52]. In line with this, MIF localization was not found at the endoplasmic reticulum or Golgi apparatus [53]. In addition, inhibition of protein transport from endoplasmic reticulum to Golgi apparatus had no effects on the LPS-induced secretion of MIF [51]. Albeit the exact mechanisms of MIF secretion still remain unclear, general vesicular transport factor p115 (also known as USO-1) [54] and one member of the ATP-binding cassette transporter (presumably ABCA1) were suggested to be involved in MIF secretion [51].

D-DT is composed of 117 amino acids with a molecular weight of 13 kDa [55–57]. D-DT shares significant homology with MIF, with 27% and 35% amino acid sequence identity in mice and humans, respectively. In fact, the 3D-structure of D-DT is nearly identical to MIF with a barrel-shaped homotrimer [58]. Similar to MIF, D-DT also conserves a vestigial enzymatic activity for converting D-dopachrome to DHICA in the vertebrate organisms [59,60].

2.2. MIF and D-DT expression

MIF is ubiquitously expressed in mammals under normal physiological conditions and found in numerous cell types, including the cells of immune, nerve, circulatory, urinary and digestive system (summarized in Table 1). In contrast to MIF, there is less published data about D-DT expression, which seems to be similar albeit not fully overlapping with MIF expression (Table 1 and Fig. 1).

Table 1
List of cell types for which MIF or D-DT expression was shown.

	Cell type	Species	Ref.
MIF	Lymphocytes	Human, mouse	[44,157]
	Monocytes/macrophages	Human, mouse	[44]
	Neutrophils	Human, mouse, rat	[38,43,158]
	Dendritic cells	Mouse	[159]
	Eosinophils	Human	[160]
	Platelets	Human, mouse	[161]
	Mast cells	Mouse	[162,163]
	Endothelial cells	Human	[164]
	Vascular smooth muscle cells	Rat	[165]
	Fibroblasts	Human	[166]
	Neurons (cortex, hippocampus, cerebellum and hypothalamus)	Mouse, rat	[167,168]
	Astrocytes	Rat	[169]
	Cardiomyocytes	Mouse	[72,170]
	Hepatocytes	Human, mouse	[11,171]
	Renal tubular epithelial cells	Human, mouse	[85]
	Parietal epithelial cells of the glomerulus	Human, mouse	[86]
	Urinary bladder epithelium	Rat	[172]
	Endometrium	Human	[173]
	Glandular epithelium of the breast	Human	[174,175]
	Anterior pituitary glandular epithelium	Mouse	[1,40]
	Chondrocytes	Human, rat	[176,177]
	Osteoblasts	Rat	[178]
	Keratinocytes	Human	[179]
	Adipocytes	Rat	[180]
	β-cells	Mouse, Rat	[181,182]
D-DT	Cardiomyocytes	Mouse	[143]
	Hepatocytes	Mouse	[22]
	Renal tubular epithelium	Mouse	[22]
	Intestinal epithelium	Mouse	[22]
	Bronchial epithelium	Mouse	[22]
	Adipocytes	Human	[183]
	Dendritic cells	Mouse	[22]
	Neurons (cortex, hippocampus, cerebellum and thalamus)	Mouse	[184]

2.3. Regulation of MIF and D-DT transcription

A 1 kb region that is proximal to the open reading frame of *MIF* gene was shown to be required for *MIF* transcription. A number of specific binding sites for different transcription factors were annotated in this region and some of them were experimentally proven to regulate *MIF* promoter activity (Summarized in Fig. 2). The basal MIF expression is regulated by the transcription factor specificity protein 1 (SP1) and cAMP response element binding protein (CREB). Two SP1 and two CREB binding sites (CRE-site) were described within the *MIF* promoter. Only the proximal SP1 specific site and the proximal CRE-site were shown to interfere with *MIF* promoter activity [61,62]. Interestingly, deletion of both proximal sites resulted in a complete abrogation of *MIF* transcription, but the effect was mild when only one of the sites was deleted. This indicates a potential cooperative regulation of MIF expression via these two transcriptional factors [61,62]. Apart from maintaining the basal *MIF* transcription, SP1 was shown to be involved in increasing *MIF* transcription level upon recognition of pathogen-associated molecular patterns. The effect was shown to be mediated by activation of mitogen-activated protein kinase 1/2 (MEK1/2), leading to the nuclear accumulation of phosphorylated SP1 followed by enhanced SP1 interaction with the *MIF* promoter which increases MIF synthesis [61].

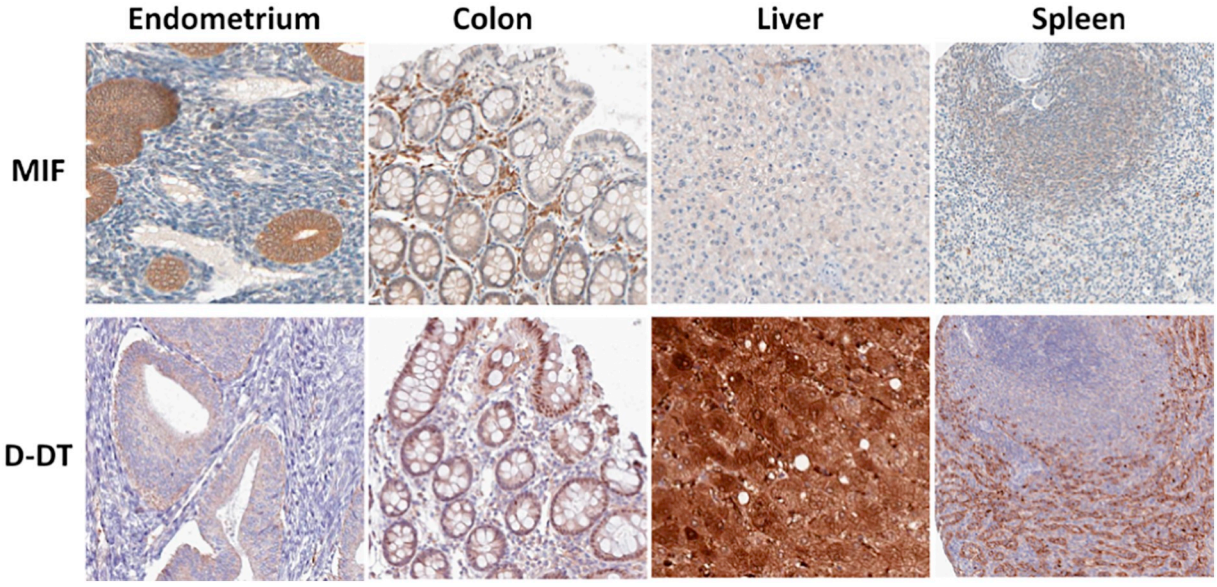

Fig. 1. Examples of differential expression of MIF and D-DT in healthy human tissue.
Immunohistochemical staining of MIF and D-DT in human endometrium, colon, liver and spleen tissue [185,186]. Data were taken from www.proteinatlas.org

A nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) binding region was also described in the *MIF* promoter region. NFκB is dispensable for the basal *MIF* transcription, but could increase *MIF* expression in vascular smooth muscle cells exposed to oxidized low-density lipoprotein [63]. Another transcription factor that could enhance *MIF* transcription level is inverted CCAAT box binding protein of 90 kDa (ICBP90, also known as UHRF1) which could bind to the 4-nucleotide microsatellite CATT repeat. Knockdown of ICBP90 abrogated the increase of *MIF* expression after LPS treatment. ICBP90 deletion also abolished the LPS-induced synthesis and secretion of interleukin (IL)-1β, IL-6, IL-8, TNF-α and monocyte chemoattractant protein (MCP)-1 to the same extent as *MIF* knockdown. Thus, ICBP90 is likely a pivotal factor mediating the pro-inflammatory response of toll-like receptor 4 (TLR4) agonist. ICBP90 was also shown to be involved in the up-regulation of *MIF* expression after TLR1/2, TLR5 and TLR9 activation. This transcription factor also mediated the basal level of *MIF* expression in untreated cells [42].

Pituitary-specific positive transcription factor 1 (PIT1) is another transcriptional factor found to bind to the CATT tetranucleotide repeats within the *MIF* promoter, albeit the functional role of PIT1/MIF promoter interaction in immune cells remains unclear [64]. Additionally, *MIF* expression and promoter activity could be triggered by hypoxia [65–67]. This was mediated by the Hypoxia-induced factor 1α (HIF1α). Putative HIF1α binding hypoxia-response element (HRE) was found in the *MIF* gene. Interestingly, CREB was shown to inhibit the HIF1α-induced *MIF* transcription under hypoxia [67], plausibly via the

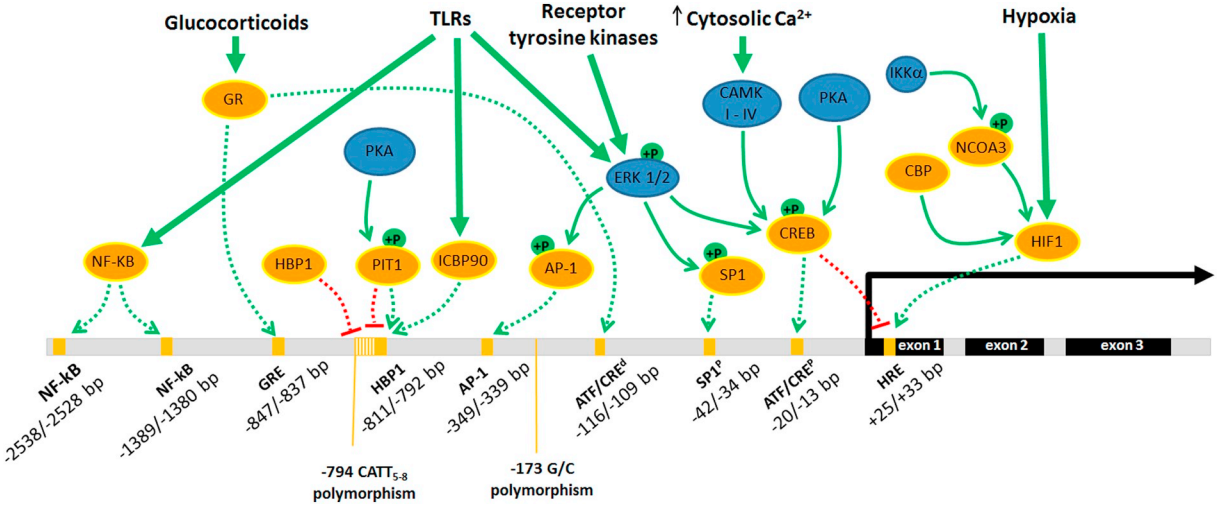

Fig. 2. Schematic representation of human *MIF* gene and its 5′-untranslated promoter region.
Putative transcription factor sites and corresponding transcription factors are shown in orange. The common polymorphism with a number of tetranucleotide CATT sequences is shown by white-orange hatching. Another common single-nucleotide polymorphism −173 G/C is marked with an orange line. SP1 and cAMP response element-binding protein (CREB) are mediating the basal *MIF* expression. Moreover, their activities increase as a result of MAPK, PKA and CAMK-dependent signaling cascades. Glucocorticoid receptor (GR) is a potent inducer of *MIF* transcription. SP1, ICBP90 and NFKB augment *MIF* transcription at the downstream of Toll-like receptors (TLRs) signaling. HIF1 augments *MIF* transcription under hypoxia. HIF1 requires assembling with NCOA3 and CBP to form a complex that upregulates *MIF* transcription. CREB inhibits HIF1-mediated transcription, possibly competing for hypoxia responsive element (HRE)-site. HMG-Box Transcription Factor 1 (HBP1) specifically reduces *MIF* transcription and shares a similar binding site for UHFR1 and PIT1 (located within −794 CATT polymorphic region). Functional outcomes of PIT1 binding to *MIF* promoter are still unknown.

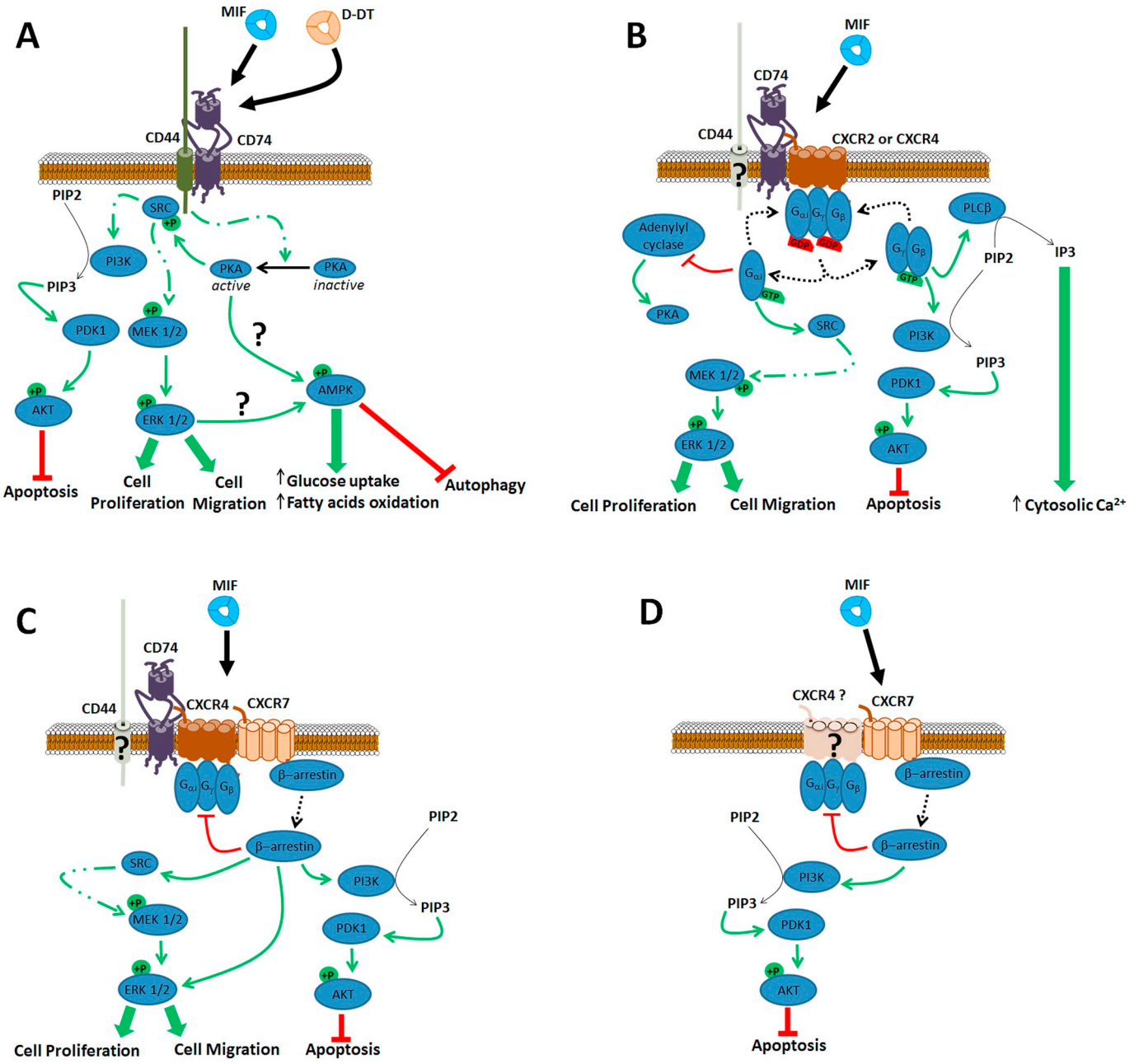

Fig. 3. MIF's and D-DT's cell surface receptor complexes.
A. MIF and D-DT signaling could be triggered by interaction with CD74 on cell surface. Interaction of CD74 and CD44 is required for signaling cascade triggering. Complex of CD74/C44 with MIF or D-DT triggers PKA activation as a first step, which phosphorylates SRC and triggers ERK1/2 and PI3K-AKT pathways. AMPK is also phosphorylated upon CD74/CD44 activation by MIF. However, the exact signaling pathway is elusive. B. MIF is also capable of binding CXCR2 or CXCR4. However, a physical interaction of CD74 with either CXCR2 or CXCR4 is required for MIF signaling transduction. If CD44 involvement is necessary it is not clear yet. A classical G-coupled protein pathway is then triggered, resulting in stimulation of ERK1/2, PI3K-AKT and PLC-beta signaling cascades. C,D. MIF serves as a ligand for CXCR7. Two pathways were described under MIF binding to CXCR7. C First one involves oligomerization of CXCR4 with CXCR7. Moreover, CXCR4 binds CD74. The role of CD44 in this receptor complex is not clear. CXCR7 recruits beta-arrestin-2 to CD74/CXCR4/CXCR4 complex. Beta-arrestin-2 inhibits G-proteins signaling by occupying their binding site on CXCR4. Moreover, beta-arrestin-2 serves as an activating scaffold for SRC, ERK1/2 and PI3K. Thus, CXCR7 is considered to switch the G-protein signaling mode of ERK1/2 activation, characterized by the short-living signals, long-standing mode of ERK1/2 pathway activation. D. MIF was shown to induce PI3K-AKT, but not ERK1/2 pathways binding to CXCR4/CXCR7 complex. Although, complexes of MIF with CXCR4 and CXCR7 were isolated by immunoprecipitation, precluding MIF binding to CXCR4 with anti-CXCR4 antibodies was not able to abolish CXCR7-depedndent PI3K-AKT activation. Due to the computational modeling, D-DT is considered not to have capacity to bind to CXCR2, −4 or −7.

interaction with the HRE [68]. Lastly, a transcriptional co-activator Nuclear receptor co-activator 3 (NCOA3, also known as SCR-3 and AIB1) is another inducer for *MIF* transcription. IκB kinase α (Ikkα) mediates the phosphorylation of NCOA3 which could bind to the HIF1α, followed by recruitment of CREB-binding protein (CBP) which binds to the HRE within *MIF* promoter region [69].

MIF transcription was found to be repressed by high mobility group (HMG)-box containing protein 1 (HBP1), as its binding sequence appears within the *MIF* promoter region. Cell lines with higher HBP1 protein expression exhibited lower MIF protein expression [70]. Methylation of cytosine residues in the GpC-sites by DNA methyltransferase is a well-described epigenetic mechanism of gene silencing.

Although *MIF* gene is located in a region that is rich in CpG-sites, their methylation was found to be an extremely rare event, suggesting that CpG-sites methylation might not be involved in the regulation of basal *MIF* expression [61].

Polymorphism in the number of CATT microsatellite repeats at the position −794 of *MIF* promoter affects its transcription. Four genotypes containing 5–8 CATT repeats are known. 5 CATT repeats genotype is associated with a lower basal *MIF* promoter activity whereas the 6, 7 or 8 CAAT repeats genotypes are associated with a higher *MIF* promoter activity [71]. Consequently, the higher number of CATT repeats was associated with a higher amount of ICBP90 bound to *MIF* promoter and an up-regulated *MIF* expression [42]. Presence of > 5 CATT repeats also leads to the enhanced MIF secretion after hypoxia [72]. In human study > 5 CATT repeats haplotype is associated with higher severity of autoimmune disease [71]. G/C polymorphism at the −173 position of *MIF* promoter region strongly correlates with the severity of many diseases [73–75].

There are only a few studies reporting the regulation of *D-DT* transcription. HRE was found to be located at the −148,-104 and + 365 positions of the *D-DT* gene. However, only one HRE at +356, i.e. between exon 1 and exon 2, was shown to be responsible for an up-regulation of *D-DT* transcription under hypoxia by HIF-1α and HIF-2α [76]. Forkhead box protein O1 (FOXO1) was shown to repress *D-DT* expression. Two FOXO1 binding sites were annotated in *D-DT* gene at −1485 and − 88 position of the promoter, and the distal site could mediate a further suppression of *D-DT* promoter activity [77].

2.4. Spontaneous phenotype in $Mif^{-/-}$ and $D\text{-}dt^{-/-}$ mice

Despite its ubiquitous expression, *MIF* deficient mice ($Mif^{-/-}$) show no spontaneous pathological phenotype at a young age. However, prematurely delivered $Mif^{-/-}$ mice at embryonic day 18 suffered from acute respiratory distress syndrome with extremely low survival rate (8%), compared to the wild-type (WT) mouse pups which exhibited less severe lung dysfunction and much higher survival rate (75%). Importantly, $Mif^{-/-}$ mice delivered at normal term demonstrate no respiratory dysfunction [78]. In line with these data, the incidence of bronchopulmonary dysplasia was lower in preterm infants with −173*C allele, a polymorphism in MIF promoter that is associated with higher MIF production [79]. Insulin resistance [80] and dilated cardiomyopathy was observed in the $Mif^{-/-}$ mice at the age of 12 and 24 months, respectively [81]. Interestingly, one study demonstrated an increased longevity in the $Mif^{-/-}$ mice [82]. To date, no spontaneous pathological phenotypes have been reported in the $D\text{-}dt^{-/-}$ mice [83,84]. A number of experimental studies demonstrated that manipulation of *Mif/D-dt* expression and their downstream signaling pathways might cause little side effects in the healthy organs [85–88]. On the other hand, studies in numerous animal models showed that MIF and D-DT exert various functions in response to a wide variety of pathological stimuli and diseases (see below).

3. MIF and D-DT receptors and signaling pathways

MIF binds to four receptors including CD74, CXCR2, CXCR4 and CXCR7 [14–16]. Among these receptors, D-DT was shown to interact with CD74 [22]. While CXCR2, −4, −7 have several other known ligands, MIF and D-DT are the only known ligands for CD74 inducing signaling. MIF receptors could be organized in four different receptor complexes: CD74/CD44 [17], CD74/CXCR2 [15], CD74/CXCR4 [20] and CD74/CXCR4/CXCR7 [16] (summarized in Fig. 3). All these four complexes were isolated by immunoprecipitation. CD74 seems to play a pivotal role for all MIF receptor complexes, as *CD74* knockdown or applying anti-CD74 antibodies eliminates the MIF effects in the cells expressing CD44, CXCR2, CXCR4 or CXCR7. However, CD74's role in mediating MIF signaling is not fully indispensable. One report demonstrated that MIF could activate phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-AKT pathway solely via CXCR7 [21]. The involvement of CD74 in triggering MIF signaling differs from those elicited by the CXCR4 and CXCR7 bona fide ligand such as stromal cell-derived factor 1 (SDF-1) [21,48]. However, CD74 is not able to mediate MIF signaling solely by itself, as it was shown in the cells lacking CD44, CXCR2 or CXCR4 expression [17,21]. Thus, CD74 is playing a role as a central hub within MIF signaling which could possibly organize receptors and aid the formation of receptor complexes.

3.1. CD74

CD74, which is also termed as invariant chain (Ii), was first described as a non-polymorphic peptide coupled with polymorphic Major Histocompatibility Complex (MHC) II [89]. CD74 is expressed in the professional antigen-presenting cells, i.e. dendritic cells, B-cells and macrophages [90]. Other cell types such as endothelial, epithelial and some mesenchymal cells can also express CD74, which is particularly enhanced by certain factors, e.g. interferon (INF)-γ [90].

Up to date, two major functions of CD74 were described as it could serve as a chaperone for MHC II and a receptor for MIF and D-DT. After protein translation, CD74 assembles to form trimers inside the endoplasmic reticulum. Most of the CD74 trimers then bind to MHC IIα- and β-chains forming a nonameric complex [91,92] which then relocates to the plasma membrane. In the $Cd74^{-/-}$ mice, the MHC II complexes are trapped in cis-Golgi or in the endoplasmic reticulum, which results in impaired antigen presentation [93,94].

CD74 is produced in a molar concentration excess compared to MHC II [95] so that the MHC II-free CD74 trimers located at the cell surface can act as receptors for MIF and D-DT. MIF binding region is located in the extracellular domain between the 109 and 149 amino acid residues of CD74 [14]. Computational modeling of the MIF/CD74 docking showed that three MIF trimers are bound to one CD74 trimer. In contrast, the computational modeling suggested that only one D-DT trimer is attached to one CD74 trimer [96,97]. (*S*,*R*)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO1) was shown to be a potent MIF inhibitor [98]. When ISO1 binds to MIF, it obscures a pivotal amino acid residue within the MIF protein for MIF/CD74 interaction (Proline-2) [98,99]. A number of different inhibitors of MIF and CD74 were described and reviewed in detail elsewhere [100,101].

Upon MIF binding, CD74 was shown to initiate downstream signaling by activation of the Src-family kinases (discussed in detail below), or by internalization and subsequent regulated intermembrane proteolysis of CD74. Both these downstream signaling events seem to be dependent on CD44 as a co-receptor or co-factor. Binding of MIF triggers CD74 internalization and delivery to the endocytic compartment [19,102]. The regulated intermembrane proteolysis of CD74 is mediated by presenilin homolog signal peptide peptidase-like 2a (SPPL2a), which is present in the lysosome/late endosome [103–105]. As a result, CD74 intracellular domain (ICD) is released to the cytosol. It was demonstrated that CD74-ICD can be translocated to the nucleus [106]. CD74-ICD interacts with the transcription factors NFκB and Runt related transcription factor (RUNX) which positively regulates their activities [107]. MIF triggers CD74-ICD formation which up-regulates the anti-apoptotic gene B-cell lymphoma-extra large (*Bcl-xl*), thereby improving the B-cell survival [19]. It is not yet clear whether this signaling pathway also plays a functional role in other cells and tissues except lymphocytes and gastrointestinal cells [108].

3.2. CD44

CD44 was identified as a co-receptor required for MIF signal transduction [17] (Fig. 3A). CD44 is a highly polymorphic protein with a number of isoforms resulting from alternative splicing. Only the full-length variant has been extensively studied. It plays an important role in lymphocyte activation, recirculation and homing, hematopoiesis,

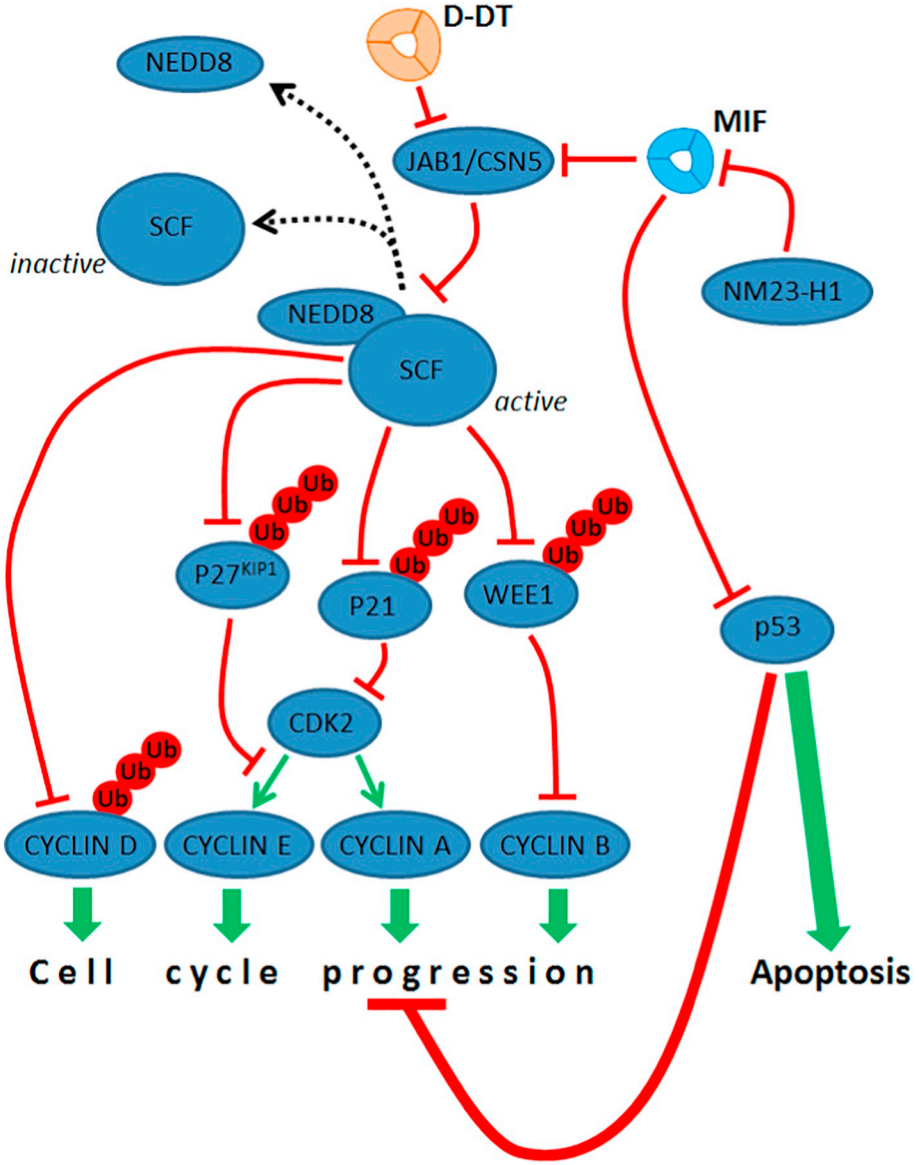

Fig. 4. MIF and D-DT signaling induced by intracellular interactions.
MIF and D-DT could bind and inhibit JAB1/CSN5 intracellularly. This preserves Skp1-Cullin1-F-box (SCF) complex in an active form, resulting in degradation of WEE1, P21 and $P27^{KIP1}$ and subsequently induce cyclin activity. MIF also binds p53 and precludes it from acting as a transcription factor. NM23-H1 binds to MIF to inhibit MIF interaction with other proteins.

and tumor metastasis [109]. CD44 serves as a receptor for hyaluronic acid, osteopontin, collagens and matrix metalloproteinases [109]. *Cd44* deletion abolished MIF signaling effect in CD74-expressing cells. It is important to note that CD74 could serve as a ligand for CD44 [110]. However, addition of MIF to the co-culture of $CD74^{+}CD44^{-}$ and $CD74^{-}CD44^{+}$ cells was not able to activate the MIF signaling, suggesting that CD74 and CD44 need to form a receptor complex in *cis* within a cell to transduce the intracellular MIF signal. Indeed, formation of CD74/CD44 complex was evident by immunoprecipitation [17,19]. Similarly, the triggering of signaling cascades upon interaction of D-DT with CD74 also requires the presence of CD44 [22].

Intra-membrane domain of CD44 is important for transduction of MIF signaling by targeting the SH2-SH3 domains of non-receptor tyrosine kinases of Src-family [19]. After the interaction of SH2-SH3 domains of Src with its CD44 binding sites, the conformation of the Src kinase is changed with subsequent liberation of its active center. In vitro, a rapid (observed already after 1 min of MIF addition) and transient (lasting for approximately 10 min) auto-phosphorylation of Tyrosine-416 of Src occurred upon MIF binding to CD74/CD44 complex. During the next 20 min, phosphatidylinositol-4,5-bisphosphate3-kinase (PI3K) and protein kinase B (AKT) were also phosphorylated and activated the corresponding downstream signaling pathways [10,19]. MIF mediates Src auto-phosphorylation which could phosphorylate Extracellular-signal Regulated Kinase (ERK1/2) in a PKA-dependent and PKC-independent manner [17]. AMPK phosphorylation was also noticed after binding of MIF to CD74/CD44 [72]. However, the exact pathway resulting in AMPK activation remains elusive (discussed in detail below). Binding of D-DT to CD74/CD44 complex also triggers the ERK1/2 signaling pathway [22] (Fig. 3A).

3.3. CXCR2, CXCR4 and CXCR7

The direct MIF binding with CXCR2 [15], CXCR4 [15], and CXCR7 [16] has been described. CXCR2, CXCR4 and CXCR7 belong to the family of CXC chemokine receptors. CXCR2 expression is mostly restricted to neutrophils and endothelium [111], CXCR4 and CXCR7 are

expressed widely in the hematopoietic cell lineage, endothelium and neuronal cells [112,113]. Activation of CXCRs is triggered via the simultaneous binding of their ligands to two different sites of the receptors. MIF shares very little sequence homology with the bona fide CXCRs ligands, e.g. CXCL8 (for CXCR2) and SDF-1 (for CXCR4 and CXCR7) but contains both motifs that are required for CXCR binding and activation upon folding into a tertiary structure. MIF/CXCR2 interaction is mediated by pseudo-ELR and N-loop-like motifs which are formed by Arginine-12 and Aspartate-45 [114], and the residues 47–56 respectively [115]. In D-DT, Alanine and Glycine are located at the position 12 and 45 respectively [116], suggesting that there is unlikely an interaction between D-DT and CXCR2, though further experimental proofs are still required.

For MIF/CXCR4 interaction, the RLR sequence of MIF at positions 87–89 is engaged [117]. The N-loop-like motif that is complementary to the second CXCR4 binding site formed from the amino acid residues 43–98 of MIF. This motif partially overlaps with that responsible for CXCR2 binding [118]. The N-loop-like motif of MIF that mediates MIF/CXCR4 interaction also contains similar amino acid residues that are required for MIF/CD74 interaction [99]. Therefore, some conventional MIF antagonists, like ISO 1, can inhibit MIF's interaction with both receptors CD74 and CXCR4 [118], but may not affect the MIF/CXCR2 binding.

Despite the structural resemblance with CXCR ligands, MIF doesn't fully mimic their signaling cascades. For instance, MIF didn't induce ERK1/2 phosphorylation in platelets (which express CXCRs but not CD74), as SDF-1 did [21,48]. MIF binds to CD74/CXCR2 and CD74/CXCR4 complexes which results in activation of the ERK1/2 [16,119] and AKT pathways [20,21] via G_i alpha subtype of G-protein (Fig. 3B). CXCR2 and CXCR4 could be internalized together with CD74 [15,120] after interaction with MIF, possibly providing an opportunity for MIF to interact with other cytoplasmic proteins (discussed in details further, see also Fig. 4). CD74 neutralization by specific antibodies eliminates MIF signaling through CXCR2 or CXCR4 [15] which shows a pivotal role of the physical interaction of CD74 and CXCR2 or CXCR4 during MIF signal transduction. Moreover, a complex of CD74/CXCR2/CXCR4 was isolated by immunoprecipitation [15,20]. However, the mechanistic explanation for how precluding MIF binding to CD74 influences the MIF interaction with CXCR2 and CXCR4 is still missing. Also, it is not known if CD44 is engaged in CD74/CXCR2, −4 dependent signaling.

CXCR7 shares same ligands with CXCR4 (SDF-1 and MIF) and forms complexes with CXCR4 [121]. CXCR7 is not coupled with any type of G-proteins, but instead with beta-arrestin-2. Hence, the signaling through CXCR4 is distinct from those via CXCR4/CXCR7 complex, as beta-arrestin-2 recruits proteins that mediate the clathrin-dependent endocytosis of receptor complexes [122]. In addition to the receptor internalization, beta-arrestin-2 could activate ERK1/2 and c-Jun N-terminal kinase 3 (JNK3) by acting as a scaffold to maintain both kinases in an active form for a long time [123,124]. Thus, CXCR7 is considered to switch the activator of ERK1/2 signaling from G-protein to beta-arrestin-2, i.e. a switch from a short-lived signaling activity to a long-lasting signal, respectively (Fig. 3C).

Surprisingly, MIF was reported to activate PI3K-AKT pathway via CXCR7 solely in platelets and the Madin-Darby Canine Kidney (MDCK) cells [21]. ERK1/2 phosphorylation, a hallmark of MIF signaling effect via CD74/CD44, CD74/CXCR4 and CD74/CXCR4/CXCR7 complexes, was not present in these cells after incubation with MIF. However, stimulation of MIF efficiently triggered AKT phosphorylation in a PKC-independent manner. Precluding MIF's interaction with CXCR4 has no effect on MIF action [21]. These findings suggest that CXCR7 could modulate MIF signaling as part of the CD74/CXCR4/CXCR7 complex or serve as a separate receptor for MIF (Fig. 3D).

3.4. MIF binding to intracellular proteins

MIF was shown to physically interact with various intracellular proteins, thereby interplaying with other signaling pathways. One of the intracellular interaction partners of MIF is the c-Jun activation domain-binding protein 1/COP9 signalosome subunit 5 (JAB1/CSN5). MIF's CXXC motif is responsible for its interaction with the Mpr1, Pad1 N-terminal (MPN) domain of JAB1/CSN5 [125,126] which could inhibit the JAB1/CSN5 activity. JAB1/CSN5 represents an important subunit of the constitutive photomorphogenic 9 signalosome complex [127]. By mediating the cleavage of Nedd8, JAB1/CSN5 acts as a negative regulator of the Skp1-Cullin1-F-box (SCF) complex. Deneddylation of SCF complex results in loss of its ubiquitination activity which stabilizes other intracellular proteins such as c-JUN, c-MYC, WEE1, p21, $p27^{Kip1}$, Cyclin E or beta-catenin [128]. JAB1/CSN5 also critically influences cell cycle progression by the deneddylation of SCF [128]. Thereby, it could be postulated that JAB1/CSN5 inhibition might be one potential mechanism underlying the cell cycle arrest induced by *MIF* deletion in some disease models [85,129] (Fig. 4). Currently, binding of MIF to JAB1/CSN5 was only noted in the conditions with excessive MIF, i.e. either after overexpression of the cytokine or addition to the cell culture media in vitro [125]. Importantly, D-DT was also shown to bind to JAB/CSN5 [22], which possibly exerts the same effect on cell cycle progress as MIF.

A *Nucleoside diphosphate kinase A* (*NME1*) gene product, NM23-H1, is another intracellular partner of MIF. NM23-H1 is abundantly expressed in the organisms [130]. Decreased expression of NM23-H1 correlates with high metastatic activity of carcinomas. It is suggested that the down-regulated NM23-H1 expression in cancer cells could facilitate metastasis [131]. MIF/NM23-H1 interaction involves the MIF's CXXC motif, thus NM23-H1 may act as a competitive inhibitor for MIF-JAB1/CSN5 interaction (Fig. 4). In line with this, overexpression of NM23-H1 abrogated cell cycle progression in *MIF*-overexpressing cells. The NM23-H1/MIF interaction also depressed the phosphorylation level of ERK1/2, AKT, serum and glucocorticoid-regulated kinase (SGK) and Bcl-2-associated death promoter (BAD) induced by MIF [132].

It has been documented that MIF could physically interact with thioredoxin-interacting protein (TXNIP). TXNIP is a potent inhibitor of NFκB regulatory gene transcription [133] as TXNIP could possibly compete with NFκB to prevent its interaction with gene promoters. TXNIP also recruits Histone deacetylase 1 (HDAC1) to deacetylate the DNA-binding region of NFκB, thereby augmenting its inhibitory effect [134]. MIF binds to TXNIP, which prevents the TXNIP/NFκB interaction. *MIF* overexpression in *TXNIP*-overexpressing cells increased the expression of *NFκB* genes, exerting anti-apoptotic (i.e. *Bcl-xL, cIAP2*) and pro-inflammatory effects (i.e. *ICAM1, uPA* and *MMP2)* [134]. MIF's interaction partners TXNIP and JAB1/CSN5 were also shown to interact with each other [135], but the role of MIF in this interaction is not completely clear.

The interaction between MIF and ribosomal protein S3 (RPS3) was described in the lung cancer cell lines [136]. This interaction affects the NFκB activity, but in contrast to MIF/TXNIP interaction, MIF/RPS3 interaction suppresses the transcriptional factor activity. Under basal conditions, MIF forms a complex with RPS3 and retains in the cytoplasm. After irradiation of cells, casein kinase (CK)-2α phosphorylates and dissociates RPS3 from MIF [136]. The liberated RPS3 then translocates into the nucleus and binds to NFκB, facilitating its transcriptional activity [136].

The nuclear p53 has been shown to interact with MIF in cancer cells [137]. This interaction precluded p53 action as a transcription factor that drives *Bax* and *p21* expression. *Mif* knockdown induced the *Bax* and *p21* expression and retarded the malignant cell proliferation [137] (Fig. 4). The p53 inhibition induced by MIF represents a potential

mechanistic link between tissue inflammation and malignant transformation [138,139].

Finally, MIF could physically interact with two proteins that participate in cell antioxidant defense: the proliferation-associated gene (PAG) [140] and the superoxide dismutase 1 (SOD1) [141]. The interaction with SOD1 was shown in vitro to prevent the formation of aggregates formed from misfolded *Sod1*^{G85R} mutant, suggesting that MIF could also play a chaperone-like role for SOD1. *Sod1*^{G85R}-*Mif*$^{-/-}$ mice exhibited decreased longevity in comparison with *Sod1*^{G85R}-*Mif*$^{+/+}$ mice, demonstrating that MIF/SOD1 interaction may also occur in vivo [142].

4. MIF-family cytokines SIGNALING in different tissues

MIF possesses a putative pro-inflammatory action by inducing the expression and release of certain pro-inflammatory cytokines. Such pro-inflammatory property could counteract with the immunosuppressive action of glucocorticoids, which increases survival of inflammatory cells and attracts immune cells to the site of injury. In addition, MIF promotes cancerogenesis by promoting the proliferation and survival of malignant cells. These data showed clearly that MIF has deleterious effects in various diseases, leading to the interest of developing MIF inhibitors for potential clinical use. However, recent data suggested that MIF and D-DT might also exert organ- and tissue-protective effects during diseases. In the next section, we review the differential tissue signaling of MIF and D-DT in the pathologies of heart and kidney, as a striking example of how different the MIF signaling could be involved in different tissues.

4.1. Heart

Both MIF and D-DT are differentially expressed in the heart. Under basal conditions, the heart muscle cells show low abundance of MIF and high abundance of D-DT [72,143]. At the age of 3 months, *Mif*$^{-/-}$ mice displayed no apparent alterations in the heart function in comparison to the wild-type (WT) littermates, as evident by the morphological or histological analyses [81,88]. No spontaneous pathological phenotype in heart was observed in *D-dt*$^{-/-}$ mice or in the mice with cardiomyocyte specific deletion of D-DT (*Myh6-Cre::Ddt*$^{fl/fl}$ mice) [22,143]. However, *Mif*$^{-/-}$ mice demonstrated worse heart contractility compared to WT mice at the age of 24 months. Such impairment of cardiac function was accompanied by more pronounced left ventricular hypertrophy and myocardial fibrosis in *Mif*$^{-/-}$ mice [81].

Further studies revealed that both MIF and D-DT could act as an endogenous protective factor. Genetic deletion or chemical inhibition of MIF or D-DT resulted in exacerbated ischemic injury [12,72,143,144]. Moreover, mice treated with MIF20, a small molecule compound which could increase MIF binding affinity to CD74, significantly decreased the myocardial infarct size and preserved cardiac function [145]. *Mif*$^{-/-}$ mice showed a more severe cardiac hypertrophy in response to pressure overload [88]. Another study showed that 48 h of food deprivation had no effect on cardiac function in WT mice, whereas the *Mif*$^{-/-}$ mice developed pronounced heart dysfunction [146]. On the contrary, exogenous MIF stimulation was shown to impair heart contractility [147], which could explain the beneficial effect of MIF neutralizing antibodies on cardiac dysfunction induced by endotoxemia or burn injury [147,148]. Addition of exogenous D-DT had no effects on myocardium contractility [143], suggesting that D-DT might be better suited as a drug target for treating ischemic heart injury.

HIF1 plays a pivotal role in the up-regulation of MIF and D-DT expression under hypoxia [12,143]. MIF expression in cardiomyocyte was also up-regulated upon exposure to oxidants [47]. MIF or D-DT was shown to be secreted from cardiomyocytes and act as an autocrine or paracrine manner [12] in CD74-dependent manner [12,72,143,145]. In contrast to other tissues, D-DT and MIF induced signaling was mediated via AMPK phosphorylation [12,72,143]. In vitro studies demonstrated that there are different signaling cascades for activating 5' AMP-activated protein kinase (AMPK) by D-DT and MIF. D-DT elicited fast, but transient increase in AMPK phosphorylation with a peak effect at 15 min post stimulation. AMPK phosphorylation was mediated by Calcium/Calmodulin dependent protein kinase kinase 2 (CaMKK2) activation and preceded by a transient increase of cytoplasmic Ca^{2+} level at 5 min after D-DT exposure [143]. In contrast, AMPK phosphorylation occurred only after 60 min of MIF incubation and lasted for 2 h [72]. These effects were dependent on the expression of CD74/CD44 receptor complex [72]. The exact mechanism for signaling transduction is not clear yet, as the activity of two vital direct upstream activators of AMPK, CAMKK2 and LKB1, were unchanged [72]. In *Cd74*$^{-/-}$ mice, AMPK phosphorylation induced by ischemia was diminished to a greater extent than either in *Mif*$^{-/-}$ or in *D-dt*$^{-/-}$ mice, suggesting there is a co-operative effect between both cytokines.

Among the downstream targets of AMPK, histone deacetylase 5 (HDAC5) and GTPase activating protein Tuberous sclerosis proteins 1 and 2 (TSC1/2) play a major role in mediating the protective effects of MIF and D-DT. HDAC5 represses transcription of the glucose transporter GLUT4 by binding to *GLUT4* transcription factor MEF-2A [149,150]. Phosphorylated HDAC5 was shown to dissociate from MEF-2A thus allowing *GLUT4* transcription [151]. The increase of GLUT4 expression enhances glucose uptake into cardiomyocytes which could act as a protective mechanism to cope with ischemia. TSC1/2 is a mTORC1 inhibitor [152] and activation of TSC1/2 AMPK via phosphorylation also triggers autophagy [153]. Under pressure-overload challenge and 48 hrs starvation, phosphorylation of AMPK was upregulated in WT mice together with subsequent increase of autophagosome biogenesis and clearance of ubiquitin adapter Sequestosome-1 (SQSTM1)/p62. In the hearts of *Mif*$^{-/-}$ mice, which were exposed to pressure-overload and 48 hrs starvation, AMPK activation and autophagy were impaired which associates with a decrease in cardiac function. Treating animals with rapamycin, a potent inhibitor of mTORC1, restored the cardiac function loss in *Mif*$^{-/-}$ mice [81,88].

Age-dependent decrease in endogenous *MIF* expression has been proposed as one potential mechanism of cardiac senescence [12,66]. However, the *Mif*$^{-/-}$ mice demonstrated an increased lifespan. It could be postulated that elimination of the pro-tumorigenic and pro-inflammatory effects of MIF could be more beneficial than MIF's protective effects in counteracting cellular senescence. However, the precise role of MIF on cardiac function still remains ambiguous. The cardioprotective effects of MIF were mostly restricted to animal models of ischemia and reperfusion with short reperfusion periods [34,72,144]. The role of MIF on cardiac function might strongly depend on the applied animal model and disease duration and on the method applied to measure cardiac function, which might explain the partially conflicting results in the literature. Moreover, in a recent epidemiological study in patients with heart failure, which constitutes a major cause of death and hospitalization in the western world, high serum levels of MIF correlated with high risk of mortality [154].

Taken together, elevated MIF expression in heart was shown to have beneficial effects by activating the AMPK pathway with subsequent improved compensatory response to an increase in energy demand and decreased blood supply. However, exogenous addition of MIF also decreases heart contractility, which may represent a dangerous side effect for patients with pre-existing heart failure.

4.2. Kidney

In contrast to the heart, no spontaneous pathological renal phenotype was found in *Mif*$^{-/-}$ mice [85–87]. However, *Mif* deletion strongly aggravated the severity of different animal models of acute and chronic kidney diseases, in particular those that are not associated with a strong (auto)inflammatory response [84,85,87]. At the same time, *Mif*$^{-/-}$ mice were protected against experimental glomerulonephritis [86] and polycystic kidney disease caused by *Pkd1* mutation [155].

Whether *D-dt*$^{-/-}$ mice demonstrate any spontaneous renal phenotype is not yet known.

Both beneficial and detrimental MIF effects seem to rely on its regulation of cell cycle progression and are cell-type specific in kidney. In an experimental glomerulonephritis which was caused by an autoimmune disease with increased proliferation of glomerular cells, *Mif* deletion abolished the pathological lesions and improved the disease course [86]. MIF stimulated proliferation of parietal epithelial cells and mesangial cells via CD74 [85,86]. Together with the anti-inflammatory effects, this explains the beneficial outcomes of MIF neutralization during immune-mediated glomerulonephritis. In contrast, *Mif* deletion is detrimental in acute and chronic renal tubulointerstitial diseases, as it might affect the regeneration of tubular cells, which is an important recovery mechanism after renal injury. Tubular cells of *Mif*$^{-/-}$ mice showed significantly less proliferative capacity and were arrested in the G2-phase of the cell cycle, which was associated with an increase of p27 expression and reduced expression of cyclin B1 and cyclin A1 [85]. These cell-cycle arrested cells produced more pro-inflammatory and pro-fibrotic cytokines such as CCL2 and PDGF-B, which aggravated renal inflammation and fibrosis [85]. MIF deficiency was also associated with a robust down-regulation of cyclin expression during ischemia/reperfusion of kidney [84]. Finally, MIF protection against acute kidney injury was also mediated via counteracting the programmed cell death of tubular cells [87].

Mif deletion was shown to be beneficial in the model of polycystic kidney disease caused by *Pkd1* mutation. This congenital pathology is characterized by uncontrolled cyst growth that eventually replaces normal renal tissue. Cyst growth was markedly retarded either in the *Mif*$^{-/-}$ mice or in the mice treated with the MIF small molecule inhibitor ISO1. The protective effect of MIF deletion in this disease seems to rely on the MIF interaction with p53. As it was mentioned above, MIF inhibits p53 thus decreases apoptosis and induces cell cycle arrest. p53 was up-regulated in the *Pdk1*-mutant cells treated with ISO1 [155]. Accordingly, *Mif*$^{-}$ deletion or treatment with ISO1 increased apoptosis in the *Pdk1*-mutant cells and this effect could be abolished by *p53* deletion. Taken together, MIF-mediated increase in tubular cell apoptosis and reduced proliferation of tubular cells seems to be renoprotective in polycystic kidney disease [155].

Tissue-specific MIF signaling can be illustrated by its downstream regulatory kinase activities in vitro. In the kidney cells, a fast (10 min after MIF addition) and transient ERK1/2 phosphorylation followed by AMPK inhibition (2 h after MIF addition) has been reported, which is in contrast to the signaling cascade elicited in the heart (see above) [155,156].

In summary, MIF and D-DT seem to have no biological effects in healthy kidneys. However, these cytokines on the one hand aggravate the progression of (auto)immune and polycystic kidney disease whereas on the other hand they ameliorate the course of acute kidney injury and renal fibrosis.

5. Conclusions

The understanding of MIF functions evolved far beyond its initial description as a pro-inflammatory chemokine-like protein at the beginning of 1930s. The additional knowledge was mainly supplemented by the generation of transgenic animal models and MIF inhibitors. Better understanding on MIF signaling mechanism has been achieved by the findings on the complexity of MIF receptors and the associated downstream signaling pathways. Such diverse mechanisms drive the multifaceted effects of MIF and D-DT in different cells, organs and diseases. It is well illustrated that MIF drives numerous inflammatory and malignant diseases. On the other hand, MIF was shown to play a protective role in mediating resistance to various infections, and accumulating evidence also suggests that MIF can exert protective effects in certain organs and diseases, particularly of the heart and the kidney. Our future effort should better delineate the disease context and cell-specific roles of MIF. Targeting MIF in specific cells and diseases could be then potentially translated into clinical practice as a therapeutic approach. The discovery of D-DT as MIF's homolog and specific ligand for CD74 opened several new exciting research fields. Overall, unraveling the complexity of MIF signaling remains an exciting area for basic, translational and clinical research.

Disclosure

The authors report no conflicts of interest.

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