Abstract. Leukemia is a group of malignant diseases of clonal hematopoietic stem-progenitor cells and its pathological mechanisms remain to be elucidated. Genetic and epigenetic abnormalities, as well as microenvironmental factors, including cytokines, serve critical roles in leukaemogenesis. Macrophage migration inhibitory factor (MIF) has been presented as one of the key regulators in tumorigenesis, angiogenesis and tumor metastasis. This article focuses on the functional role of MIF and its pathway in cancer, particularly in leukemia. MIF/CD74 interaction serves prominent roles in tumor cell survival, such as upregulating BCL-2 and CD84 expression, and activating receptor-type tyrosine phosphatase ζ. Furthermore, MIF upregulation forms a pro-tumor microenvironment in response to hypoxia-induced factors and promotes pro-inflammatory cytokine production. Additionally, polymorphisms of the MIF promoter sequence are associated with leukemia development. MIF signal-targeted early clinical trials show positive results. Overall, these efforts provide a promising means for intervention in leukemia.

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1. Introduction

The term leukemia collectively describes a group of malignant clonal diseases of hematopoietic stem-progenitor cells, which present with various diverse and biological subtypes (1). Due to chromosomal abnormalities and genetic alterations, these cells expand in an oligoclonal manner and invade the bloodstream and extramedullary tissues (2). Epidemiologic cross-sectional research performed in 2012 revealed that the worldwide age-standardized incidence of leukemia was 5.6 per 100,000 in men and 3.9 in women, ranking it as the 11th most prevalent with the 10th highest mortality among all cancers, with even higher numbers for specific subtypes among young and elderly patients (3). According to the World Health Organization standard classification (4), four subtypes of leukemia are recognized, based on their progression state and the affected cell lineage: Acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL).

For decades, genetic aberrations have been considered to serve an essential role in the pathogenesis of leukemia (5-7). These mutations can be categorized into three main functional groups regulating cellular activities: Mutation genes encoding transcription factors, epigenetic modifiers regulating gene expression and genes associated with signaling pathway activation. In AML, pro-proliferative signaling pathways, such
as the RAS/RAF, Janus kinase/STAT, PI3K/AKT signaling pathways, are aberrantly activated as a result of gene mutations, including mutations of fms related receptor tyrosine kinase 3, KIT proto-oncogene, receptor tyrosine kinase, RAS family members and serine/threonine kinases (7). In lymphoid leukemia, the most commonly mutated gene is NOTCH1, and this contributes to NOTCH1 signaling pathway activation (6). BCR activator of RhoGEF and GTPase-ABL proto-oncogene 1, non-receptor tyrosine kinase, the key fusion gene of CML, leads to tyrosine kinases deregulation (6). Apart from gene mutation, epigenetic regulators also serve essential roles in leukaemogenesis. For example, DNA methyltransferase 3α, tet methylcytosine dioxygenase 2, isocitrate dehydrogenase [NADP(+)]1, methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit and FTO α-ketoglutarate dependent dioxygenase, have been reported to be involved in pathological DNA methylation and mRNA modification in AML (10,11). These efforts have been well described in other reviews. Although progress has been made in the treatment of leukemia, especially in terms of the use of tyrosine kinase inhibitors (12) and immunotherapy (13,14), the disease remains incurable, either due to frequent relapse or refractory cases, and the best-practice treatment regiments are still being identified.

Extrinsic signals from the bone marrow (BM) micro-environment promoting leukaemogenesis provide novel mechanisms in treating leukemia (15,16). Inflammation mediator-related genes, and specifically expressed proteins, serve a vital role in the pathogenesis of various tumor diseases, including breast cancer, gastrointestinal tumors and genitourinary cancers (17,18). It is widely accepted that the activity of inflammatory factors, especially when causing chronic inflammation, can result in a pro-tumor microenvironment, promoting tumor survival, proliferation and metastasis (17-19). Among these, macrophage migration inhibitory factor (MIF) is one of the pro-inflammatory cytokines, which is upregulated in a number of autoimmune diseases (20), as well as in cancer (21), including leukemia (22). Its multiple functions are necessary for cell proliferation, survival and invasion (23), suggesting this protein could be a promising candidate therapeutic target. This review focuses on the function of MIF in general and its role in cancer, and on how these functions influence the development of leukemia.

2. MIF structure and physiology

MIF has been characterized as a pleiotropic, multifunctional, pro-inflammatory factor (28). First identified in the 1930s (29), MIF was recognized as a soluble immune cell-derived factor in 1966 and was first cloned in 1989 (26,30). Notably, MIF acts as an endogenous regulator of glucocorticoids (31). Under normal conditions, MIF can be detected in the serum at a range of 2-6 ng/ml, following the circadian rhythm of glucocorticoids (31). The main sources of MIF are anterior pituitary cells, where a pre-secreted form is stored in the cytoplasm (31). Serum levels of MIF peak 2-3 h before relative serum levels of steroids reach their peak (32). Apart from pituitary cells, different types of cells, including monocytes/macrophages, granulocytes, dendritic cells, endothelial cells and mesenchymal cells, can secret MIF in response to inflammatory stimuli (33-36). The MIF protein lacks an N-terminal secretion signal (37,38). Instead, its release is partly dependent on Golgi-associated protein p115 (38) or exosomes (39).

3. MIF signaling pathways

Several signaling pathways in which MIF is involved have been identified in the past decades (Fig. 1). The interaction between MIF and the CD74/CD44 complex was a landmark discovery (40,41). CD74, which is also known as constant chain protein, is a molecular marker expressed on the cell surface (40). It belongs to the major histocompatibility complex (MHC) II invariant chain and facilitates the interaction of MHC II-antigen peptides for antigen presentation (42). Multiple studies have demonstrated that CD74 is upregulated in different types of cancer cells (43-45). CD44 is an adhesion molecule that mediates the activation of SRC proto-oncogene, non-receptor tyrosine kinase (Src) family proteins (46). Notably, half of the exons of the gene encoding CD44 can be spliced into different subtypes, to generate different protein ectodomains (46). As a result, MIF-activated CD44 is expressed in cells with dynamic proliferation, such as epithelial and tumor cells (46). CD44 can be recruited by CD74 to form a CD74/CD44 complex, which is involved in the activation of downstream signaling pathways (47).

First, the interaction of MIF-CD74/CD44 results in phosphorylation of Src family proteins (41). Subsequently, the phosphorylated Src proteins activate the ERK1/2 MAPK signaling pathway by phosphorylation (41), accompanied by the activation of cytosolic phospholipase A2 (cPLA2) and the inhibition of p53, which is associated with anti-apoptosis and proliferation effects (48,49). MIF acts as a negative regulator of p53, probably via binding to p53 and MDM2 proto-oncogene (an E3 ubiquitin ligase), to form a ternary compound (50,51). Its phosphorylated Src proteins activate the ERK1/2 MAPK signaling pathway by phosphorylation (41). Subsequently, the phosphorylated Src proteins activate the ERK1/2 MAPK signaling pathway by phosphorylation (41), accompanied by the activation of cytosolic phospholipase A2 (cPLA2) and the inhibition of p53, which is associated with anti-apoptosis and proliferation effects (48,49).
chemokine receptor type 2 (CXCR2)/CXCR4 (56), which is associated with cell migration and inflammation (57) (blue arrow; Fig. 1). Thirdly, MIF can promote the cleavage of CD74 to produce CD74-ICD (grey arrow), which is considered to provide a further activation signal. When MIF interaction activates NF-κB and inhibits p53 by stabilizing the MIF-MDM2-p53 ternary complex, it leads to the upregulation of the expression of proteins of the BCL-2 family, such as BCL-2, BCL-X and MCL-1, which promotes cell survival and proliferation. In addition, MIF can regulate the cell cycle by facilitating Rb phosphorylation. CXCR, C-X-C chemokine receptor; MDM2, MDM2 proto-oncogene; MIF, macrophage migration inhibitory factor; SPPL2A, signal peptide peptidase like 2A; Src, SRC proto-oncogene, non-receptor tyrosine kinase; CD74-ICD, CD74 intracellular domain; p, phosphorylated; cPLA2, cytosolic phospholipase A2; Rb, retinoblastoma protein; E2F, adenoviral early region 2 binding factor; MCL-1, MCL1 apoptosis regulator, BCL2 family member.

Figure 1. MIF signaling pathways. MIF induces Src family phosphorylation by binding to the CD74/CD44 complex or CXCR2/4 (blue arrow), and further activates downstream ERK1/2 MAPK or PI3K/AKT signaling pathways. The interaction of MIF and CD74 can also promote the cleavage of CD74 to produce CD74-ICD (grey arrow), which is considered to provide a further activation signal. When MIF interaction activates NF-κB and inhibits p53 by stabilizing the MIF-MDM2-p53 ternary complex, it leads to the upregulation of the expression of proteins of the BCL-2 family, such as BCL-2, BCL-X and MCL-1, which promotes cell survival and proliferation. In addition, MIF can regulate the cell cycle by facilitating Rb phosphorylation. CXCR, C-X-C chemokine receptor; MDM2, MDM2 proto-oncogene; MIF, macrophage migration inhibitory factor; SPPL2A, signal peptide peptidase like 2A; Src, SRC proto-oncogene, non-receptor tyrosine kinase; CD74-ICD, CD74 intracellular domain; p, phosphorylated; cPLA2, cytosolic phospholipase A2; Rb, retinoblastoma protein; E2F, adenoviral early region 2 binding factor; MCL-1, MCL1 apoptosis regulator, BCL2 family member.

4. MIF and hematopoiesis

Hematopoietic homeostasis is maintained by the hematopoietic stem cells (HSCs) and the hematopoietic microenvironment (62). HSCs stay in the BM niche, a special structure within the BM that can be considered as a complex ecological system (62). The niche is composed of different types of cells that interact with HSCs, providing signals by secretion of supporting factors to regulate blood cell production (63). For example, stem cell factor, TGF-β1, platelet factor 4 [also referred to as chemokine (C-X-C motif) ligand 4] and angiopoietin 1 are all factors that maintain HSC quiescent status (63), whereas stromal-derived factor 1 (also referred to as C-X-C motif chemokine ligand 12) and its receptor CXCR4 (64,65), or adhesion molecules, such as vascular cell
adhesion protein 1 (66), are necessary for cell migration and homing. In addition, IL-7 (67) and erythropoietin (68) facilitate HSC proliferation and differentiation.

CD74 is an important regulator involved in the maturation and differentiation of B cells, and MIF participates in regulation of B cell differentiation and survival. Gore et al (55) reported that the CD74/CD44 complex was found in the membrane of murine B cells, activating downstream signaling in the classical MIF-CD74 interaction described in the previous section. Furthermore, dendritic cells in the BM facilitate B cell survival in a MIF-dependent manner (69). However, to the best of our knowledge, whether MIF is involved in the differentiation and proliferation of HSCs has not yet been established and this requires further study.

5. MIF and leukaemogenesis

Hypoxia-induced factors (HIFs) include a heterodimeric transcription factor whose classical activation is oxygen concentration-dependent (70). BM is distinguished by high cellularity and low oxygen concentrations, albeit being supplied by a complex vascular network (71). Extrinsic factors, such as stem cell factors, further promote increased levels of HIF proteins (72). In the leukemic BM, increased cellularity and high metabolic activity of proliferating cells further reduce oxygen concentrations and are associated with increased expression levels of HIF factors, mainly HIF-1α (73-75), which are involved in a number of pro-tumor processes, such as cell proliferation and differentiation, metabolism, and angiogenesis (76-79). Hypoxia is an important factor in the upregulation of MIF (80), and HIF-1α can induce MIF expression (81) in a p53-dependent manner (82), while the secretion of MIF can in turn promote the activation of HIF-related signaling pathways, forming a positive feedback loop (83).

In addition, the leukemic BM niche allows clonal proliferation of pre-leukemia HSCs and leukemic stem cells, while reducing the capacity of supporting normal hematopoiesis (15). This partly results from BM structure changes, such as endostrral stroma remodeling and fibrosis (84). Additionally, the increased inflammatory signaling also contributes to leukaemogenesis (85), again resulting in MIF signaling. The functions of MIF in the different subtypes of leukemia are reviewed in the next section.

6. Functions of MIF in leukemia

CLL. CLL comprises a group of chronic lymphoproliferative disorders. Its prevalence is higher in Caucasians compared with Asian, Caribbean or African populations (9). It is characterized by malignant mature B cell proliferation and accumulation (9).

It has been demonstrated that MIF can be upregulated in solid tumors (86-89). As early as in 1979, increased levels of MIF were described in sera from patients with CLL, especially in patients with advanced stages (22). CD74, the main receptor of MIF, is also upregulated in response to its upregulated ligand secreted by CLL cells (90). Binsky et al (90) reported that MIF acts as a pro-survival factor in CLL. MIF/CD74 interaction activates downstream IL-8 secretion in an autocrine manner, as has been demonstrated in vitro, and this upregulates BCL-2 levels via the PI3K/AKT signaling pathway (90). This can be reversed by (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester, a nontoxic inhibitor of MIF, and by anti-IL-8 antibodies, suggesting that the MIF/CD74 signaling pathway promotes anti-apoptosis (90). In addition, the MIF/CD74 signaling pathway can promote CLL survival by upregulating the expression of midkine, which is a pro-tumor protein (90). Midkine binds to its receptor receptor-type tyrosine phosphatase ζ, mediating anti-apoptotic activity (91). Another target participating in MIF signaling is CSD4, a member of the signaling lymphocyte activation molecule immunoglobulin superfamily, which modulates the function of immune cells (92). Upon upstream stimulation, CD84 recruits its ligand SH2 domain containing 1B to activate the AKT signaling pathway and promote the activation of anti-apoptotic molecules (92).

Reinart et al (93) crossed MIF+ mice with Eμ-TCL1 mice, creating an animal model to verify the function of MIF in CLL. Compared with wild-type animals, the MIF knockout mice exhibited a delayed onset of disease and longer survival of CLL (93). Notably, the authors identified a reduced infiltration of tumor-associated macrophages (TAMs) in the spleen of the mice, indicating that recruitment of TAMs is associated with MIF expression (93). A recent study revealed that knockout of CD74 in Eμ-TCL1 mice has no significant effect on CLL development, possibly as a result of yet unknown compensatory mechanisms, which need to be further investigated (94). MIF is also able to increase the viability of CLL by stimulating the production of very late antigen-4 integrin (VLA-4), a homing factor, via TAp63 (95). The upregulated VLA-4 allows CLL to remain and survive in BM (95).

AML. AML is a heterogeneous group of diseases characterized by myeloid progenitor cells with abnormal proliferation and differentiation (96). Similar to CLL, the serum levels of MIF are increased in AML compared with healthy bodies (97). This indicates that the presence of MIF in the microenvironment may serve an important role in the pathogenesis of AML. In 2014, by studying BM samples from 85 patients with AML or myelodysplastic syndromes, Falantes et al (80) demonstrated that MIF was highly expressed in BM, which was consistent with the levels in peripheral blood. Higher MIF expression was associated with a poorer prognosis and less sensitivity to azacitidine (80), a first-line therapeutic drug of AML. A mechanistic explanation was provided by Abdul-Aziz et al (45), whose in vitro work deepened the understanding of the role of MIF in AML. They described that MIF is secreted by AML blasts, after which it interacts with CD74 via protein kinase C β, but not CXCR2, and thus, this induces IL-8 expression in BM mesenchymal stromal cells, which may then promote AML survival (45). Subsequently, they demonstrated that HIF modulates MIF expression in response to a hypoxic BM microenvironment. Indeed, knockdown of HIF1α or MIF prolongs the life of xenograft mice, suggesting that HIF1α promotes MIF expression and enhances AML blast survival (98). This process is shown in Fig. 2.

Somatic mutations have been identified in different AML phenotypes, and are associated with response to therapy and subsequent relapse (99). MIF promotes the survival of AML-blasts carrying the lysine methyltransferase 2A-MLLT3 super elongation complex subunit mutation (99). Future
As a result, AML-derived MIF upregulates IL-8 expression in BM-MSCs via ways, which in turn facilitates MIF expression in a positive loop (grey arrow).

HIF expression, activating HIF1α in the bone marrow of AML, the local hypoxic microenvironment promotes HIF expression, activating HIF1α associated with downstream signal pathways, which in turn facilitates MIF expression in a positive loop (grey arrow). AML-derived MIF upregulates IL-8 expression in BM-MSCs via the MIF/CD74/PKCβ signaling pathway. In turn, IL-8 promotes AML cell survival and proliferation (black arrow). MIF, macrophage migration inhibitor factor; HIF, hypoxia-inducible factor; AML, acute myeloid leukemia; BM-MSC, bone marrow mesenchymal stromal cells; PKCβ, protein kinase Cβ; p, phosphorylated.

Figure 2. MIF function in modulating pro-tumor microenvironment in AML.

In the bone marrow of AML, the local hypoxic microenvironment promotes HIF expression, activating HIF1α associated with downstream signal pathways, which in turn facilitates MIF expression in a positive loop (grey arrow). As a result, AML-derived MIF upregulates IL-8 expression in BM-MSCs via the MIF/CD74/PKCβ signaling pathway. In turn, IL-8 promotes AML cell survival and proliferation (black arrow). MIF, macrophage migration inhibitor factor; HIF, hypoxia-inducible factor; AML, acute myeloid leukemia; BM-MSC, bone marrow mesenchymal stromal cells; PKCβ, protein kinase Cβ; p, phosphorylated.

studies are required to identify the association between other mutations or subtypes of AML and MIF expression, as their identification would have potential in precision medical care.

ALL. ALL is characterized by proliferation of malignant lymphoid precursor cells, mainly caused by genetic alterations (8). Two types are recognized, T-cell acute lymphoblastic leukaemia (T-ALL) and B-cell acute lymphoblastic leukaemia, depending on the lymphoid precursor cells involved (8). During treatment of ALL, the administration of glucocorticoids is important in all phases (8). However, glucocorticoid resistance weakens the effects of treatment (100). MIF counteracts the function of steroids by suppressing NF-κB inhibitor IκB and reversing cPLA2 activity (48,101). In vitro data suggest that MIF expression in a CEM cell line was not affected by treatment with glucocorticoids (102). A polymorphism near the MIF promoter (details provided in the next section) is associated with ALL prognosis, and its mechanism remains to be elucidated.

7. Genetics of MIF in leukemia

In rheumatic diseases, regulation of the MIF gene has been widely discussed (103,104). It has been identified that there are two polymorphic sequences located on the MIF promoter (103,104). One is caused by a microsatellite (CATT) present in 5-8 copies at location -794 (-794CATT<sub>5-8</sub>) (104) and the other by a G/C polymorphism at location -173 (-173G/C) (Fig. 3) (105). To the best of our knowledge, the function of the -173G/C polymorphism is still unknown. Abrerrant expression levels of genes, such as carnitine palmitoyltransferase 1A, are associated with poor prognosis (106). Sharaf-EIdein et al (107) identified a negative association between MIF serum levels and ALL prognosis and also reported a higher incidence of the C genotype over the G genotype in children with ALL compared with healthy children (108). These results were corroborated in a Chinese study (109). Apart from ALL cases, the -173G/C polymorphism may also be involved in patients with AML (110). The -173C allele is associated with higher MIF serum levels and poses a risk factor for deteriorative prognosis (106). However, MIF can be upregulated in other diseases (56,111-113) except leukemia, resulting in a low specificity for leukemia. MIF could be recognized as a prognostic biomarker instead of as a diagnostic marker in leukemia.

For the promoter polymorphism at -794CATT<sub>5-8</sub>, it has been demonstrated that higher numbers of the CATT repeat result in higher MIF secretion (104). The number of repeats is also associated with the severity of a number of autoimmune diseases and the efficacy of using corticosteroids (114,115); however, to the best of our knowledge, its role in leukemia has not yet been reported. The frequency of -173C has been identified to be associated with presence of 7 CATT repeats at -794 (103). Notably, ubiquitin like with PHD and ring finger domains 1 (UHRF1), also known as inverted CCAAT box-binding protein of 90 kDa, is highly expressed in a variety of tumor cells, including in lung cancer and hepatocellular carcinoma (116-118) and promotes tumorigenesis (119). Therefore, UHRF1 can be considered to be a proto-oncogene. Our previous study demonstrated that the UHRF1 acts as a transcription factor that binds to the CATT<sub>5-8</sub> motif (120). UHRF1 regulates MIF transcriptional activity in a CATT<sub>5-8</sub> length-dependent manner (120). Our recent study revealed that UHRF1 acts as a positive regulator mediating MIF expression in T-ALL by interacting with CATT repeats, leading to T-ALL survival (121). This provides one more piece of evidence regarding how MIF transcription and activity can be involved in the onset or progression of leukemia.

8. Potential therapeutic targets

In the past few decades, the treatment of leukemia has greatly improved and developments are still ongoing (122). Taking CLL as an example, a clinical trial (CALGB 9712) demonstrated that the combination of rituximab and fludarabine improved the rate of complete response, due to cytotoxic synergism (123). Although various types of drugs, such as anti-CD20 monoclonal antibody (mAb) (124,125), B cell receptor signaling kinase inhibitors (126) and BCL-2 antagonists (127), have been applied in clinical practice, other possible targets remain to be identified in order to improve treatment response and efficacy.

Three main types of drugs target the MIF/CD74 signaling pathway: MIF inhibitors, mAb targeting MIF and CD74 (128). In hematopoietic tumors, anti-CD74 mAbs
exhibited promising therapeutic potential. Milatuzumab, an anti-CD74 humanized murine mAb, is generated by grafting of antigen-recognizing variable regions of LL1 onto human IgG1 (129). Hertlein et al (130) demonstrated that milatuzumab mediates cytotoxicity on CLL directly via CD74 expression. Furthermore, clinical data described promising results for treatment of refractory patients with CLL (131). The data from a phase I trial conducted by Martin et al (132) revealed an improvement of WBC count (usually elevated in leukemia) from an average of 91x10⁹ cells/l to a nadir of 32x10⁹ cells/l, despite short clinical benefits. A phase I-II study from Israel revealed that milatuzumab improved the treatment response in 62.5% (5/8) of patients, with a decreased spleen size and a decreased requirement of packed red cell transfusion (133). Researchers have also identified that the amounts of lymphocytes and platelets are increased, while circulating levels of BCL-2 are decreased, as a result of treatment with milatuzumab (133). For safety, neutropenia, thrombocytopenia and rash are the most common treatment-related adverse events in a dose-dependent manner (132). The Israel study indicated that infection was the most common adverse event but was not associated with milatuzumab (133). It may have resulted from the generation situation of enrolled individuals (133). The efficacy of the drug has also been demonstrated in multiple myeloma (134). More evidence is required based on larger, randomized clinical trials, as well as trials in other subtypes of leukemia.

Although treatment options have greatly improved over time, AML treatment remains a great challenge, due to the complicated genetic alterations and immunophenotypes responsible for this disease (135). Recent studies have provided novel insights on combination treatments with immune checkpoint inhibitors and hypomethylating agents (136), targeting tumor-associated metabolic and energetic signaling pathways (137), although more clinical data are required to support such a treatment strategy.

Notably, in hematopoietic tumors, UHRF1 expression is associated with tumor aggressiveness (138). Alhosin et al (139) reported that thymoquinone could induce apoptosis in ALL cells, at least in vitro, in a p73-dependent manner. Other research suggests that UHRF1 facilitates the degradation of promyelocytic leukemia (PML) protein (140). Knockdown of UHRF1 could restore PML protein expression and inhibit cell migration and capillary formation in vitro (140). Furthermore, UHRF1 stabilizes receptor tyrosine kinase-like orphan receptor 1 in pre-B cells of ALL, which decreases the sensitivity to chemotherapy (141). Our previous study also suggested that UHRF1 acts as pro-tumor factor by promoting T-ALL cell survival (121). Further investigations could focus on whether UHRF1 can be used as a potential therapeutic target.

9. Conclusions

The various functions of MIF go far beyond its initial description as a pro-inflammatory chemical kinase-like protein in the early 1930s. This improved understanding of its complex and multiple functions is enabled and supported by in vitro experiments and investigations using transgenic animal models, often in combination with MIF inhibitors. An improved understanding of the relevant MIF signaling mechanisms in leukemia can be obtained by studying the complex MIF interactions with various receptors and their downstream signaling pathways, which may eventually provide a novel platform for therapeutic strategies in the future.

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