Macrophage migration inhibitory factor in the pathogenesis of leukemia (Review)

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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.

Contents

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Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; BM-MSCs, bone marrow mesenchymal stromal cells; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; cPLA2, cytosolic phospholipase A2; CXCR2, C-X-C chemokine receptor type 2; E2F, adenoviral early region 2 binding factor; HIF, hypoxia-induced factor; HSCs, hematopoietic stem cells; mAb, monoclonal antibody; ICBP90, inverted CCAAT box-binding protein of 90 kDa; MIF, macrophage migration inhibitory factor; PML, promyelocytic leukemia; Rb, retinoblastoma protein; TAMs, tumor-associated macrophages; VLA-4, very late antigen-4 integrin

Key words: MIF, leukemia, ICBP90, IL-8, MAPK, AKT

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 (8,9). 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) microenvironment 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 is a soluble symmetrical homotrimer (37.5 kDa), consisting of three small (115 amino acids long) 12.5 kDa monomers (24). The protein is evolutionary highly conserved, resulting in homologies >80% among protein sequences of different species, including bacteria, plants, protozoa and other non-mammals (25). Notably, MIF executes tautomerase activity and catalyzes the conversion of D-isomer of 2-carboxy-2,3-dihydroindole-5,6-quinone (D-dopachrome) to 5,6-dihydroxyindole-2-carboxylic acid (26). Its main, although not sole, receptor is CD74 (27). Binding depends on the protein-protein interaction between the N-terminal proline residue of the active site of MIF and the type II transmembrane CD74 receptor (27).

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). As a result, cell cycle arrest is repressed, increasing the risk of malignant transformation (52). MIF also affects the retinoblastoma protein-adenoviral early region 2 binding factor complex by antagonizing Rb-mediated suppression of DNA replication by upregulating expression of cyclin D1 (53,54), which progresses the cell cycle from the G_1 phase into the S phase, thus promoting cell proliferation (54). In addition, the PI3K/AKT and NF-κB signaling pathways are involved in the downstream signaling, promoting cell survival and proliferation (55). Secondly, MIF can also initiate downstream signals in a non-covalent manner following binding to C-X-C

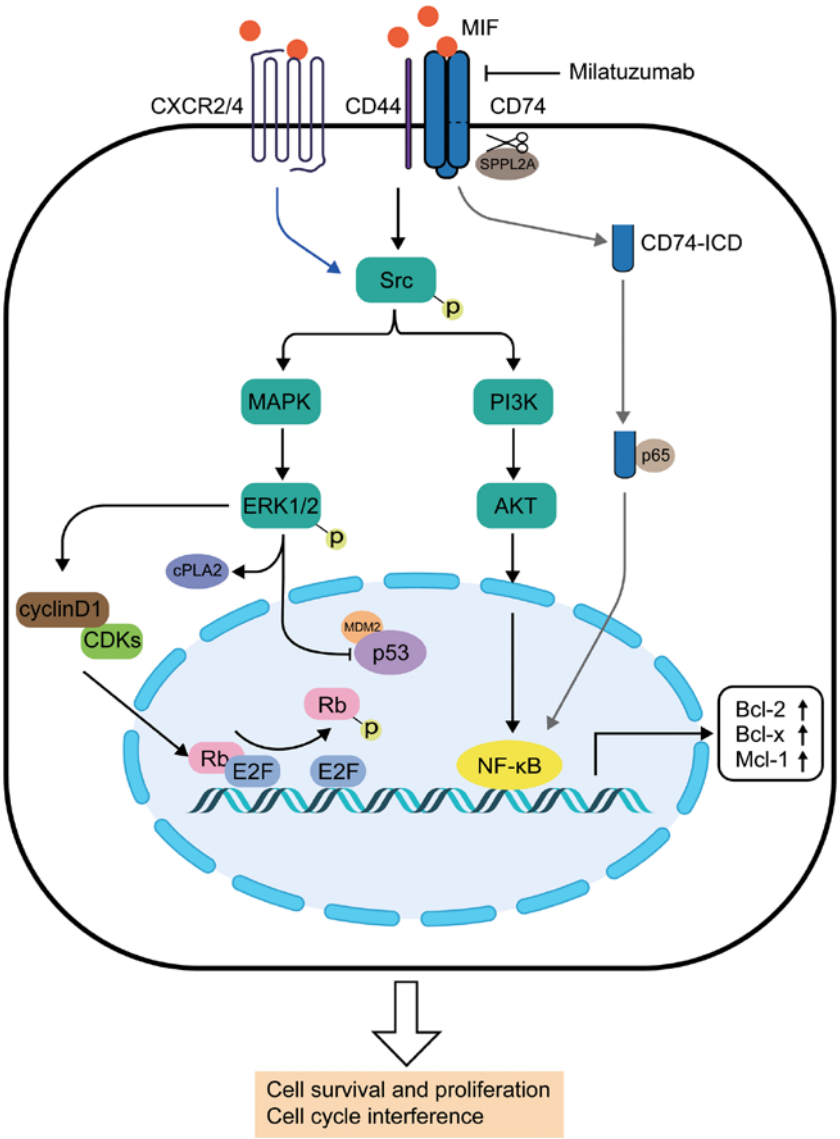

Figure 1. MIF signaling pathways. MIF induces Src family phosphorylation by binding to the CD74/CD44 complex or CXCR2/4 (blue arrow), and further activates downstream ERK1/2 MAPK or PI3K/AKT signaling pathways. The interaction of MIF and CD74 can also promote the cleavage of CD74 to produce CD74-ICD (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.

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 the intermembrane part of CD74 via sPPLA2 protease, resulting in a 42 amino acid peptide (CD74-ICD) (58). Subsequently, CD74-ICD migrates into the cytosol and binds to p65 (an NF-κB family member), regulating the transcription of NF-κB in the nucleus (grey arrows; Fig. 1) (59). It has been identified that the cleavage of CD74-ICD and NF-κB activation occurs in B cell maturation via upregulation of TAp63 (59). In addition, the tyrosine kinase receptor c-Met is involved, as it contributes to B cell proliferation and survival (60). Lastly, research suggests that a soluble form of CD74 is involved in the regulation of MIF activation (61); however, its mechanism needs to be further elucidated.

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 leukaemic stem cells, while reducing the capacity of supporting normal hematopoiesis (15). This partly results from BM structure changes, such as endostral 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 CD84, 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

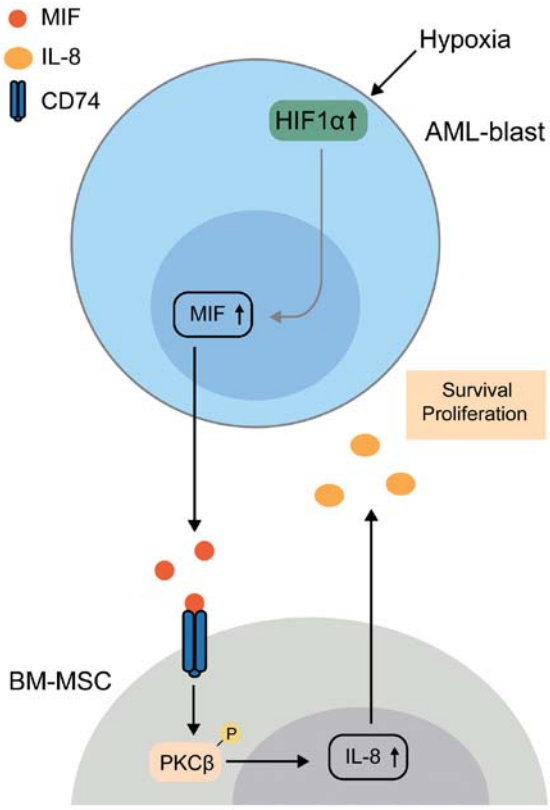

Figure 2. MIF function in modulating pro-tumor microenvironment in AML. In the bone marrow of AML, the local hypoxic microenvironment promotes HIF expression, activating HIF1α associated with downstream signal pathways, which in turn facilitates MIF expression in a positive loop (grey arrow). As a result, 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 inhibitory factor; HIF, hypoxia-induced factor; AML, acute myeloid leukemia; BM-MSC, bone marrow mesenchymal stromal cells; PKCβ, protein kinase C β; 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 leukemia, 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 (-794$CATT_{5-8}$) (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. Aberrant expression levels of genes, such as carnitine palmitoyltransferase 1A, are associated with poor prognosis (106). Sharaf-Eldein *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 -794$CATT_{5-8}$, 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 $CATT_{5-8}$ motif (120). UHRF1 regulates MIF transcriptional activity in a $CATT_{5-8}$ 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

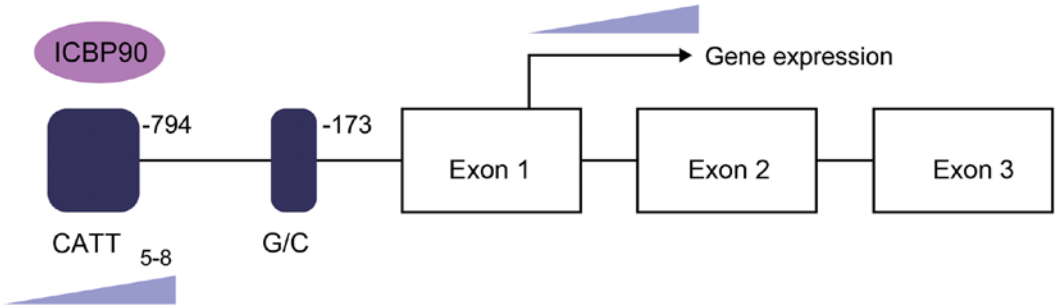

Figure 3. Gene expression of MIF. Two MIF promoter polymorphisms ($CATT_{5-8}$ and G/C) are located at positions -794 and -173, respectively. MIF transcription is activated in a MIF allele-dependent manner ($CATT_{5-8}$), which is regulated by ICBP90. ICBP90, inverted CCAAT box-binding protein of 90 kDa; MIF, macrophage migration inhibitory factor.

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 $91x10^9$ cells/l to a nadir of $32x10^9$ 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 aggression (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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Authors' contributions

JY contributed to the concept of the review. YL and XW searched the associated studies. XW drafted the document

and YL wrote the study. JS and JY supervised the study. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Saracci R and Wild CP: Fifty years of the international agency for research on cancer (1965 to 2015). Int J Cancer 138: 1309-1311, 2016.
2. Chen J, Odenike O and Rowley JD: Leukaemogenesis: More than mutant genes. Nat Rev Cancer 10: 23-36, 2010.
3. Miranda-Filho A, Pineros M, Ferlay J, Soerjomataram I, Monnereau A and Bray F: Epidemiological patterns of leukaemia in 184 countries: A population-based study. Lancet Haematol 5: e14-e24, 2018.
4. Cazzola M: Introduction to a review series: The 2016 revision of the WHO classification of tumors of hematopoietic and lymphoid tissues. Blood 127: 2361-2364, 2016.
5. Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, Kluth S, Bozic I, Lawrence M, Böttcher S, *et al*: Mutations driving CLL and their evolution in progression and relapse. Nature 526: 525-530, 2015.
6. Apperley JF: Chronic myeloid leukaemia. Lancet 385: 1447-1459, 2015.
7. Bullinger L, Döhner K and Döhner H: Genomics of acute myeloid leukemia diagnosis and pathways. J Clin Oncol 35: 934-946, 2017.
8. Malard F and Mohty M: Acute lymphoblastic leukaemia. Lancet 395: 1146-1162, 2020.
9. Bosch F and Dalla-Favera R: Chronic lymphocytic leukaemia: From genetics to treatment. Nat Rev Clin Oncol 16: 684-701, 2019.
10. Figueroa ME, Lugthart S, Li Y, Erpelinck-Verschueren C, Deng X, Christos PJ, Schifano E, Booth J, van Putten W, Skrabanek L, *et al*: DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia. Cancer Cell 17: 13-27, 2010.
11. Vu LP, Cheng Y and Kharas MG: The biology of m^6A RNA methylation in normal and malignant hematopoiesis. Cancer Discov 9: 25-33, 2019.
12. Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, Borthakur G, Pemmaraju N, Daver N, Jain P, *et al*: Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: Analysis of patient data from six prospective clinical trials. Lancet Haematol 2: e186-e193, 2015.
13. Porter DL, Hwang WT, Frey NV, Lacey SF, Shaw PA, Loren AW, Bagg A, Marcucci KT, Shen A, Gonzalez V, *et al*: Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 7: 303ra139, 2015.
14. Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, Sommermeyer D, Melville K, Pender B, Budiarto TM, *et al*: CD19 CAR-T cells of defined $CD4^+$:$CD8^+$ composition in adult B cell ALL patients. J Clin Invest 126: 2123-2138, 2016.
15. Schepers K, Campbell TB and Passegue E: Normal and leukemic stem cell niches: Insights and therapeutic opportunities. Cell Stem Cell 16: 254-267, 2015.
16. Yamashita M, Dellorusso PV, Olson OC and Passegué E: Dysregulated haematopoietic stem cell behaviour in myeloid leukaemogenesis. Nat Rev Cancer 20: 365-382, 2020.
17. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C and Flavell RA: Inflammation-induced cancer: Crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 13: 759-771, 2013.
18. Greten FR and Grivennikov SI: Inflammation and cancer: Triggers, mechanisms, and consequences. Immunity 51: 27-41, 2019.
19. Coussens LM, Zitvogel L and Palucka AK: Neutralizing tumor-promoting chronic inflammation: A magic bullet? Science 339: 286-291, 2013.
20. Kang I and Bucala R: The immunobiology of MIF: Function, genetics and prospects for precision medicine. Nat Rev Rheumatol 15: 427-437, 2019.
21. Bucala R and Donnelly SC: Macrophage migration inhibitory factor: A probable link between inflammation and cancer. Immunity 26: 281-285, 2007.
22. Benjamin D, Aderka D, Livni E, Joshua H, Shaklai M and Pinkhas J: Migration inhibition factor activity in sera of patients with chronic lymphatic leukemia. J Natl Cancer Inst 63: 1175-1177, 1979.
23. Nobre CC, de Araújo JM, Fernandes TA, Cobucci RN, Lanza DC, Andrade VS and Fernandes JV: Macrophage migration inhibitory factor (MIF): Biological activities and relation with cancer. Pathol Oncol Res 23: 235-244, 2017.
24. Sun HW, Bernhagen J, Bucala R and Lolis E: Crystal structure at 2.6-A resolution of human macrophage migration inhibitory factor. Proc Natl Acad Sci USA 93: 5191-5196, 1996.
25. Sparkes A, De Baetselier P, Roelants K, De Trez C, Magez S, Van Ginderachter JA, Raes G, Bucala R and Stijlemans B: The non-mammalian MIF superfamily. Immunobiology 222: 473-482, 2017.
26. Bloom BR and Bennett B: Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science 153: 80-82, 1966.
27. Pantouris G, Syed MA, Fan C, Rajasekaran D, Cho TY, Rosenberg EM Jr, Bucala R, Bhandari V and Lolis EJ: An Analysis of MIF structural features that control functional activation of CD74. Chem Biol 22: 1197-1205, 2015.
28. Harris J, VanPatten S, Deen NS, Al-Abed Y and Morand EF: Rediscovering MIF: New tricks for an old cytokine. Trends Immunol 40: 447-462, 2019.
29. Rich AR and Lewis MR: The nature of allergy in tuberculosis as revealed by tissue culture studies. Bull Johns Hopkins Hosp 50: 115-131, 1932.
30. David JR: Delayed hypersensitivity in vitro: Its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc Natl Acad Sci USA 56: 72-77, 1966.
31. Bernhagen J, Calandra T, Mitchell RA, Martin SB, Tracey KJ, Voelter W, Manogue KR, Cerami A and Bucala R: MIF is a pituitary-derived cytokine that potentiates lethal endotoxaemia. Nature 365: 756-759, 1993.
32. Petrovsky N, Socha L, Silva D, Grossman AB, Metz C and Bucala R: Macrophage migration inhibitory factor exhibits a pronounced circadian rhythm relevant to its role as a glucocorticoid counter-regulator. Immunol Cell Biol 81: 137-143, 2003.
33. Calandra T, Bernhagen J, Mitchell RA and Bucala R: The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. J Exp Med 179: 1895-1902, 1994.
34. Bacher M, Metz CN, Calandra T, Mayer K, Chesney J, Lohoff M, Gemsa D, Donnelly T and Bucala R: An essential regulatory role for macrophage migration inhibitory factor in T-cell activation. Proc Natl Acad Sci USA 93: 7849-7854, 1996.
35. Daryadel A, Grifone RF, Simon HU and Yousefi S: Apoptotic neutrophils release macrophage migration inhibitory factor upon stimulation with tumor necrosis factor-alpha. J Biol Chem 281: 27653-27661, 2006.
36. Calandra T and Roger T: Macrophage migration inhibitory factor: A regulator of innate immunity. Nat Rev Immunol 3: 791-800, 2003.
37. Mitchell R, Bacher M, Bernhagen J, Pushkarskaya T, Seldin MF and Bucala R: Cloning and characterization of the gene for mouse macrophage migration inhibitory factor (MIF). J Immunol 154: 3863-3870, 1995.
38. Merk M, Baugh J, Zierow S, Leng L, Pal U, Lee SJ, Ebert AD, Mizue Y, Trent JO, Mitchell R, *et al*: The Golgi-associated protein p115 mediates the secretion of macrophage migration inhibitory factor. J Immunol 182: 6896-6906, 2009.
39. Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, *et al*: Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol 17: 816-826, 2015.

40. Leng L, Metz CN, Fang Y, Xu J, Donnelly S, Baugh J, Delohery T, Chen Y, Mitchell RA and Bucala R: MIF signal transduction initiated by binding to CD74. J Exp Med 197: 1467-1476, 2003.
41. Shi X, Leng L, Wang T, Wang W, Du X, Li J, McDonald C, Chen Z, Murphy JW, Lolis E, *et al*: CD44 is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex. Immunity 25: 595-606, 2006.
42. Henne C, Schwenk F, Koch N and Möller P: Surface expression of the invariant chain (CD74) is independent of concomitant expression of major histocompatibility complex class II antigens. Immunology 84: 177-182, 1995.
43. Starlets D, Gore Y, Binsky I, Haran M, Harpaz N, Shvidel L, Becker-Herman S, Berrebi A and Shachar I: Cell-surface CD74 initiates a signaling cascade leading to cell proliferation and survival. Blood 107: 4807-4816, 2006.
44. Choi JW, Kim Y, Lee JH and Kim YS: CD74 expression is increased in high-grade, invasive urothelial carcinoma of the bladder. Int J Urol 20: 251-255, 2013.
45. Abdul-Aziz AM, Shafat MS, Mehta TK, Di Palma F, Lawes MJ, Rushworth SA and Bowles KM: MIF-induced stromal PKCβ/IL8 is essential in human acute myeloid leukemia. Cancer Res 77: 303-311, 2017.
46. Ponta H, Sherman L and Herrlich PA: CD44: From adhesion molecules to signalling regulators. Nat Rev Mol Cell Biol 4: 33-45, 2003.
47. Yoo SA, Leng L, Kim BJ, Du X, Tilstam PV, Kim KH, Kong JS, Yoon HJ, Liu A, Wang T, *et al*: MIF allele-dependent regulation of the MIF coreceptor CD44 and role in rheumatoid arthritis. Proc Natl Acad Sci USA 113: E7917-E7926, 2016.
48. Mitchell RA, Metz CN, Peng T and Bucala R: Sustained mitogen-activated protein kinase (MAPK) and cytoplasmic phospholipase A2 activation by macrophage migration inhibitory factor (MIF). Regulatory role in cell proliferation and glucocorticoid action. J Biol Chem 274: 18100-18106, 1999.
49. Mitchell RA, Liao H, Chesney J, Fingerle-Rowson G, Baugh J, David J and Bucala R: Macrophage migration inhibitory factor (MIF) sustains macrophage proinflammatory function by inhibiting p53: Regulatory role in the innate immune response. Proc Natl Acad Sci USA 99: 345-350, 2002.
50. Jung H, Seong HA and Ha H: Critical role of cysteine residue 81 of macrophage migration inhibitory factor (MIF) in MIF-induced inhibition of p53 activity. J Biol Chem 283: 20383-20396, 2008.
51. Jankauskas SS, Wong DWL, Bucala R, Djudjaj S and Boor P: Evolving complexity of MIF signaling. Cell Signal 57: 76-88, 2019.
52. Hafner A, Bulyk ML, Jambhekar A and Lahav G: The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol 20: 199-210, 2019.
53. Liao H, Bucala R and Mitchell RA: Adhesion-dependent signaling by macrophage migration inhibitory factor (MIF). J Biol Chem 278: 76-81, 2003.
54. Petrenko O and Moll UM: Macrophage migration inhibitory factor MIF interferes with the Rb-E2F pathway. Mol Cell 17: 225-236, 2005.
55. Gore Y, Starlets D, Maharshak N, Becker-Herman S, Kaneyuki U, Leng L, Bucala R and Shachar I: Macrophage migration inhibitory factor induces B cell survival by activation of a CD74-CD44 receptor complex. J Biol Chem 283: 2784-2792, 2008.
56. Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, Dewor M, Georgiev I, Schober A, Leng L, *et al*: MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. Nat Med 13: 587-596, 2007.
57. Nagarsheth N, Wicha MS and Zou W: Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol 17: 559-572, 2017.
58. Schneppenheim J, Dressel R, Hüttl S, Lüllmann-Rauch R, Engelke M, Dittmann K, Wienands J, Eskelinen EL, Hermans-Borgmeyer I, Fluhrer R, *et al*: The intramembrane protease SPPL2a promotes B cell development and controls endosomal traffic by cleavage of the invariant chain. J Exp Med 210: 41-58, 2013.
59. Lantner F, Starlets D, Gore Y, Flaishon L, Yamit-Hezi A, Dikstein R, Leng L, Bucala R, Machluf Y, Oren M and Shachar I: CD74 induces TAp63 expression leading to B-cell survival. Blood 110: 4303-4311, 2007.
60. Gordin M, Tesio M, Cohen S, Gore Y, Lantner F, Leng L, Bucala R and Shachar I: c-Met and its ligand hepatocyte growth factor/scatter factor regulate mature B cell survival in a pathway induced by CD74. J Immunol 185: 2020-2031, 2010.
61. Assis DN, Leng L, Du X, Zhang CK, Grieb G, Merk M, Garcia AB, McCrann C, Chapiro J, Meinhardt A, *et al*: The role of macrophage migration inhibitory factor in autoimmune liver disease. Hepatology 59: 580-591, 2014.
62. Morrison SJ and Scadden DT: The bone marrow niche for haematopoietic stem cells. Nature 505: 327-334, 2014.
63. Wilson A, Laurenti E and Trumpp A: Balancing dormant and self-renewing hematopoietic stem cells. Curr Opin Genet Dev 19: 461-468, 2009.
64. Sugiyama T, Kohara H, Noda M and Nagasawa T: Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 25: 977-988, 2006.
65. Ding L and Morrison SJ: Haematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. Nature 495: 231-235, 2013.
66. Papayannopoulou T, Craddock C, Nakamoto B, Priestley GV and Wolf NS: The VLA4/VCAM-1 adhesion pathway defines contrasting mechanisms of lodgement of transplanted murine hemopoietic progenitors between bone marrow and spleen. Proc Natl Acad Sci USA 92: 9647-9651, 1995.
67. Cordeiro Gomes A, Hara T, Lim VY, Herndler-Brandstetter D, Nevius E, Sugiyama T, Tani-Ichi S, Schlenner S, Richie E, Rodewald HR, *et al*: Hematopoietic stem cell niches produce lineage-instructive signals to control multipotent progenitor differentiation. Immunity 45: 1219-1231, 2016.
68. Koury MJ and Bondurant MC: Erythropoietin retards DNA breakdown and prevents programmed death in erythroid progenitor cells. Science 248: 378-381, 1990.
69. Sapoznikov A, Pewzner-Jung Y, Kalchenko V, Krauthgamer R, Shachar I and Jung S: Perivascular clusters of dendritic cells provide critical survival signals to B cells in bone marrow niches. Nat Immunol 9: 388-395, 2008.
70. Wang GL and Semenza GL: Purification and characterization of hypoxia-inducible factor 1. J Biol Chem 270: 1230-1237, 1995.
71. Parmar K, Mauch P, Vergilio JA, Sackstein R and Down JD: Distribution of hematopoietic stem cells in the bone marrow according to regional hypoxia. Proc Natl Acad Sci USA 104: 5431-5436, 2007.
72. Semenza GL: Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol 9: 47-71, 2014.
73. Wellmann S, Guschmann M, Griethe W, Eckert C, von Stackelberg A, Lottaz C, Moderegger E, Einsiedel HG, Eckardt KU, Henze G and Seeger K: Activation of the HIF pathway in childhood ALL, prognostic implications of VEGF. Leukemia 18: 926-933, 2004.
74. Frolova O, Samudio I, Benito JM, Jacamo R, Kornblau SM, Markovic A, Schober W, Lu H, Qiu YH, Buglio D, *et al*: Regulation of HIF-1α signaling and chemoresistance in acute lymphocytic leukemia under hypoxic conditions of the bone marrow microenvironment. Cancer Biol Ther 13: 858-870, 2012.
75. Chen H, Shen Y, Gong F, Jiang Y and Zhang R: HIF-α promotes chronic myelogenous leukemia cell proliferation by upregulating p21 expression. Cell Biochem Biophys 72: 179-183, 2015.
76. Kim JW, Tchernyshyov I, Semenza GL and Dang CV: HIF-1-mediated expression of pyruvate dehydrogenase kinase: A metabolic switch required for cellular adaptation to hypoxia. Cell Metab 3: 177-185, 2006.
77. Han ZB, Ren H, Zhao H, Chi Y, Chen K, Zhou B, Liu YJ, Zhang L, Xu B, Liu B, *et al*: Hypoxia-inducible factor (HIF)-1 alpha directly enhances the transcriptional activity of stem cell factor (SCF) in response to hypoxia and epidermal growth factor (EGF). Carcinogenesis 29: 1853-1861, 2008.
78. Rey S and Semenza GL: Hypoxia-inducible factor-1-dependent mechanisms of vascularization and vascular remodelling. Cardiovasc Res 86: 236-242, 2010.
79. Magliulo D and Bernardi R: HIF-α factors as potential therapeutic targets in leukemia. Expert Opin Ther Targets 22: 917-928, 2018.
80. Falantes JF, Trujillo P, Piruat JI, Calderón C, Márquez-Malaver FJ, Martín-Antonio B, Millán A, Gómez M, González J, Martino ML, *et al*: Overexpression of GYS1, MIF, and MYC is associated with adverse outcome and poor response to azacitidine in myelodysplastic syndromes and acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 15: 236-244, 2015.
81. Baugh JA, Gantier M, Li L, Byrne A, Buckley A and Donnelly SC: Dual regulation of macrophage migration inhibitory factor (MIF) expression in hypoxia by CREB and HIF-1. Biochem Biophys Res Commun 347: 895-903, 2006.

82. Oda S, Oda T, Nishi K, Takabuchi S, Wakamatsu T, Tanaka T, Adachi T, Fukuda K, Semenza GL and Hirota K: Macrophage migration inhibitory factor activates hypoxia-inducible factor in a p53-dependent manner. PLoS One 3: e2215, 2008.
83. Gaber T, Schellmann S, Erekul KB, Fangradt M, Tykwinska K, Hahne M, Maschmeyer P, Wagegg M, Stahn C, Kolar P, *et al*: Macrophage migration inhibitory factor counterregulates dexamethasone-mediated suppression of hypoxia-inducible factor-1 alpha function and differentially influences human CD4$^+$ T cell proliferation under hypoxia. J Immunol 186: 764-774, 2011.
84. Schepers K, Pietras EM, Reynaud D, Flach J, Binnewies M, Garg T, Wagers AJ, Hsiao EC and Passegué E: Myeloproliferative neoplasia remodels the endosteal bone marrow niche into a self-reinforcing leukemic niche. Cell Stem Cell 13: 285-299, 2013.
85. Meisel M, Hinterleitner R, Pacis A, Chen L, Earley ZM, Mayassi T, Pierre JF, Ernest JD, Galipeau HJ, Thuille N, *et al*: Microbial signals drive pre-leukaemic myeloproliferation in a Tet2-deficient host. Nature 557: 580-584, 2018.
86. Richard V, Kindt N and Saussez S: Macrophage migration inhibitory factor involvement in breast cancer (review). Int J Oncol 47: 1627-1633, 2015.
87. Soumoy L, Kindt N, Ghanem G, Saussez S and Journe F: Role of macrophage migration inhibitory factor (MIF) in melanoma. Cancers (Basel) 11: 529, 2019.
88. Penticuff JC, Woolbright BL, Sielecki TM, Weir SJ and Taylor JA III: MIF family proteins in genitourinary cancer: Tumorigenic roles and therapeutic potential. Nat Rev Urol 16: 318-328, 2019.
89. Zhang H, Duan J and Wu O: The expression of macrophage migration inhibitory factor in the non-small cell lung cancer. Saudi J Biol Sci 27: 1527-1532, 2020.
90. Binsky I, Haran M, Starlets D, Gore Y, Lantner F, Harpaz N, Leng L, Goldenberg DM, Shvidel L, Berrebi A, *et al*: IL-8 secreted in a macrophage migration-inhibitory factor- and CD74-dependent manner regulates B cell chronic lymphocytic leukemia survival. Proc Natl Acad Sci USA 104: 13408-13413, 2007.
91. Cohen S, Shoshana OY, Zelman-Toister E, Maharshak N, Binsky-Ehrenreich I, Gordin M, Hazan-Halevy I, Herishanu Y, Shvidel L, Haran M, *et al*: The cytokine midkine and its receptor RPTPζ regulate B cell survival in a pathway induced by CD74. J Immunol 188: 259-269, 2012.
92. Binsky-Ehrenreich I, Marom A, Sobotta MC, Shvidel L, Berrebi A, Hazan-Halevy I, Kay S, Aloshin A, Sagi I, Goldenberg DM, *et al*: CD84 is a survival receptor for CLL cells. Oncogene 33: 1006-1016, 2014.
93. Reinart N, Nguyen PH, Boucas J, Rosen N, Kvasnicka HM, Heukamp L, Rudolph C, Ristovska V, Velmans T, Mueller C, *et al*: Delayed development of chronic lymphocytic leukemia in the absence of macrophage migration inhibitory factor. Blood 121: 812-821, 2013.
94. Barthel R, Fedorchenko O, Velmans T, Rosen N, Nguyen PH, Reinart N, Florin A, Herling M, Hallek M and Fingerle-Rowson G: CD74 is dispensable for development of chronic lymphocytic leukemia in Eμ-TCL1 transgenic mice. Leuk Lymphoma 61: 2799-2810, 2020.
95. Binsky I, Lantner F, Grabovsky V, Harpaz N, Shvidel L, Berrebi A, Goldenberg DM, Leng L, Bucala R, Alon R, *et al*: TAp63 regulates VLA-4 expression and chronic lymphocytic leukemia cell migration to the bone marrow in a CD74-dependent manner. J Immunol 184: 4761-4769, 2010.
96. Short NJ, Rytting ME and Cortes JE: Acute myeloid leukaemia. Lancet 392: 593-606, 2018.
97. Islam M, Mohamed EH, Esa E, Kamaluddin NR, Zain SM, Yusoff YM, Assenov Y, Mohamed Z and Zakaria Z: Circulating cytokines and small molecules follow distinct expression patterns in acute myeloid leukaemia. Br J Cancer 117: 1551-1556, 2017.
98. Abdul-Aziz AM, Shafat MS, Sun Y, Marlein CR, Piddock RE, Robinson SD, Edwards DR, Zhou Z, Collins A, Bowles KM and Rushworth SA: HIF1α drives chemokine factor pro-tumoral signaling pathways in acute myeloid leukemia. Oncogene 37: 2676-2686, 2018.
99. Hyrenius-Wittsten A, Pilheden M, Sturesson H, Hansson J, Walsh MP, Song G, Kazi JU, Liu J, Ramakrishan R, Garcia-Ruiz C, *et al*: De novo activating mutations drive clonal evolution and enhance clonal fitness in KMT2A-rearranged leukemia. Nat Commun 9: 1770, 2018.
100. Polak R, de Rooij B, Pieters R and den Boer ML: B-cell precursor acute lymphoblastic leukemia cells use tunneling nanotubes to orchestrate their microenvironment. Blood 126: 2404-2414, 2015.
101. Daun JM and Cannon JG: Macrophage migration inhibitory factor antagonizes hydrocortisone-induced increases in cytosolic IkappaBalpha. Am J Physiol Regul Integr Comp Physiol 279: R1043-R1049, 2000.
102. Leng L, Wang W, Roger T, Merk M, Wuttke M, Calandra T and Bucala R: Glucocorticoid-induced MIF expression by human CEM T cells. Cytokine 48: 177-185, 2009.
103. Zhong XB, Leng L, Beitin A, Chen R, McDonald C, Hsiao B, Jenison RD, Kang I, Park SH, Lee A, *et al*: Simultaneous detection of microsatellite repeats and SNPs in the macrophage migration inhibitory factor (MIF) gene by thin-film biosensor chips and application to rural field studies. Nucleic Acids Res 33: e121, 2005.
104. Baugh JA, Chitnis S, Donnelly SC, Monteiro J, Lin X, Plant BJ, Wolfe F, Gregersen PK and Bucala R: A functional promoter polymorphism in the macrophage migration inhibitory factor (MIF) gene associated with disease severity in rheumatoid arthritis. Genes Immun 3: 170-176, 2002.
105. Donn RP, Shelley E, Ollier WE and Thomson W; British Paediatric Rheumatology Study Group: A novel 5'-flanking region polymorphism of macrophage migration inhibitory factor is associated with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 44: 1782-1785, 2001.
106. Shi J, Fu H, Jia Z, He K, Fu L and Wang W: High expression of CPT1A predicts adverse outcomes: A potential therapeutic target for acute myeloid leukemia. EBioMedicine 14: 55-64, 2016.
107. Sharaf-Eldein M, Elghannam D, Elderiny W and Abdel-Malak C: Prognostic implication of MIF gene expression in childhood acute lymphoblastic leukemia. Clin Lab 64: 1429-1437, 2018.
108. Sharaf-Eldein M, Elghannam D and Abdel-Malak C: MIF-173G/C (rs755622) polymorphism as a risk factor for acute lymphoblastic leukemia development in children. J Gene Med 20: e3044, 2018.
109. Xue Y, Xu H, Rong L, Lu Q, Li J, Tong N, Wang M, Zhang Z and Fang Y: The MIF -173G/C polymorphism and risk of childhood acute lymphoblastic leukemia in a Chinese population. Leuk Res 34: 1282-1286, 2010.
110. Ramireddy L, Lin CY, Liu SC, Lo WY, Hu RM, Peng YC and Peng CT: Association study between macrophage migration inhibitory factor-173 polymorphism and acute myeloid leukemia in Taiwan. Cell Biochem Biophys 70: 1159-1165, 2014.
111. Donnelly SC, Haslett C, Reid PT, Grant IS, Wallace WA, Metz CN, Bruce LJ and Bucala R: Regulatory role for macrophage migration inhibitory factor in acute respiratory distress syndrome. Nat Med 3: 320-323, 1997.
112. Donn RP, Plant D, Jury F, Richards HL, Worthington J, Ray DW and Griffiths CE: Macrophage migration inhibitory factor gene polymorphism is associated with psoriasis. J Invest Dermatol 123: 484-487, 2004.
113. De la Cruz-Mosso U, Bucala R, Palafox-Sánchez CA, Parra-Rojas I, Padilla-Gutiérrez JR, Pereira-Suárez AL, Rangel-Villalobos H, Vázquez-Villamar M, Angel-Chávez LI and Muñoz-Valle JF: Macrophage migration inhibitory factor: association of -794 CATT5-8 and -173 G>C polymorphisms with TNF-α in systemic lupus erythematosus. Hum Immunol 75: 433-439, 2014.
114. Radstake TR, Sweep FC, Welsing P, Franke B, Vermeulen SH, Geurts-Moespot A, Calandra T, Donn R and van Riel PL: Correlation of rheumatoid arthritis severity with the genetic functional variants and circulating levels of macrophage migration inhibitory factor. Arthritis Rheum 52: 3020-3029, 2005.
115. Vivarelli M, D'Urbano LE, Insalaco A, Lunt M, Jury F, Tozzi AE, Ravelli A, Martini A, Donn R and De Benedetti F: Macrophage migration inhibitory factor (MIF) and oligoarticular juvenile idiopathic arthritis (o-JIA): Association of MIF promoter polymorphisms with response to intra-articular glucocorticoids. Clin Exp Rheumatol 25: 775-781, 2007.
116. Mousli M, Hopfner R, Abbady AQ, Monté D, Jeanblanc M, Oudet P, Louis B and Bronner C: ICBP90 belongs to a new family of proteins with an expression that is deregulated in cancer cells. Br J Cancer 89: 120-127, 2003.
117. Liu YZ, Jiang YY, Wang BS, Hao JJ, Shang L, Zhang TT, Cao J, Xu X, Zhan QM and Wang MR: A panel of protein markers for the early detection of lung cancer with bronchial brushing specimens. Cancer Cytopathol 122: 833-841, 2014.

118. Fu H, Xing F, Lv Y, Zeng B, You P and Liu J: ICBP90 mediates Notch signaling to facilitate human hepatocellular carcinoma growth. Tissue Cell 54: 65-71, 2018.
119. Hopfner R, Mousli M, Jeltsch JM, Voulgaris A, Lutz Y, Marin C, Bellocq JP, Oudet P and Bronner C: ICBP90, a novel human CCAAT binding protein, involved in the regulation of topoisomerase IIalpha expression. Cancer Res 60: 121-128, 2000.
120. Yao J, Leng L, Sauler M, Fu W, Zheng J, Zhang Y, Du X, Yu X, Lee P and Bucala R: Transcription factor ICBP90 regulates the MIF promoter and immune susceptibility locus. J Clin Invest 126: 732-744, 2016.
121. Yao J, Luo Y, Zeng C, He H and Zhang X: UHRF1 regulates the transcriptional repressor HBP1 through MIF in T acute lymphoblastic leukemia. Oncol Rep 46: 131, 2021.
122. Wolach O and Stone RM: Optimal therapeutic strategies for mixed phenotype acute leukemia. Curr Opin Hematol 27: 95-102, 2020.
123. Woyach JA, Ruppert AS, Heerema NA, Peterson BL, Gribben JG, Morrison VA, Rai KR, Larson RA and Byrd JC: Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: Long-term follow-up of CALGB study 9712. J Clin Oncol 29: 1349-1355, 2011.
124. Cartron G, de Guibert S, Dilhuydy MS, Morschhauser F, Leblond V, Dupuis J, Mahe B, Bouabdallah R, Lei G, Wenger M, *et al*: Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: Final data from the phase 1/2 GAUGUIN study. Blood 124: 2196-2202, 2014.
125. Byrd JC, Flynn JM, Kipps TJ, Boxer M, Kolibaba KS, Carlile DJ, Fingerle-Rowson G, Tyson N, Hirata J and Sharman JP: Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood 127: 79-86, 2016.
126. Chang BY, Francesco M, De Rooij MF, Magadala P, Steggerda SM, Huang MM, Kuil A, Herman SE, Chang S, Pals ST, *et al*: Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. Blood 122: 2412-2424, 2013.
127. Souers AJ, Leverson JD, Boghaert ER, Ackler SL, Catron ND, Chen J, Dayton BD, Ding H, Enschede SH, Fairbrother WJ, *et al*: ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 19: 202-208, 2013.
128. Bilsborrow JB, Doherty E, Tilstam PV and Bucala R: Macrophage migration inhibitory factor (MIF) as a therapeutic target for rheumatoid arthritis and systemic lupus erythematosus. Expert Opin Ther Targets 23: 733-744, 2019.
129. Stein R, Qu Z, Cardillo TM, Chen S, Rosario A, Horak ID, Hansen HJ and Goldenberg DM: Antiproliferative activity of a humanized anti-CD74 monoclonal antibody, hLL1, on B-cell malignancies. Blood 104: 3705-3711, 2004.
130. Hertlein E, Triantafillou G, Sass EJ, Hessler JD, Zhang X, Jarjoura D, Lucas DM, Muthusamy N, Goldenberg DM, Lee RJ and Byrd JC: Milatuzumab immunoliposomes induce cell death in CLL by promoting accumulation of CD74 on the surface of B cells. Blood 116: 2554-2558, 2010.
131. Berkova Z, Tao RH and Samaniego F: Milatuzumab-a promising new immunotherapeutic agent. Expert Opin Investig Drugs 19: 141-149, 2010.
132. Martin P, Furman RR, Rutherford S, Ruan J, Ely S, Greenberg J, Coleman M, Goldsmith SJ and Leonard JP: Phase I study of the anti-CD74 monoclonal antibody milatuzumab (hLL1) in patients with previously treated B-cell lymphomas. Leuk Lymphoma 56: 3065-3070, 2015.
133. Haran M, Mirkin V, Braester A, Harpaz N, Shevetz O, Shtreiter M, Greenberg S, Mordich O, Amram O, Binsky-Ehrenreich I, *et al*: A phase I-II clinical trial of the anti-CD74 monoclonal antibody milatuzumab in frail patients with refractory chronic lymphocytic leukaemia: A patient based approach. Br J Haematol 182: 125-128, 2018.
134. Kaufman J, Niesvizky R, Stadtmauer EA, Chanan-Khan A, Siegel D, Horne H, Teoh N, Leoni MJ, Wegener W and Goldenberg DM: First trial of humanized anti-CD74 monoclonal antibody (MAb), milatuzumab, in multiple myeloma. Blood 112: 3697, 2008.
135. Döhner H, Wei AH and Löwenberg B: Towards precision medicine for AML. Nat Rev Clin Oncol, May 18, 2021 (Epub ahead of print).
136. Stahl M and Goldberg AD: Immune checkpoint inhibitors in acute myeloid leukemia: Novel combinations and therapeutic targets. Curr Oncol Rep 21: 37, 2019.
137. Rashkovan M and Ferrando A: Metabolic dependencies and vulnerabilities in leukemia. Genes Dev 33: 1460-1474, 2019.
138. Simonetti G, Padella A, do Valle IF, Fontana MC, Fonzi E, Bruno S, Baldazzi C, Guadagnuolo V, Manfrini M, Ferrari A, *et al*: Aneuploid acute myeloid leukemia exhibits a signature of genomic alterations in the cell cycle and protein degradation machinery. Cancer 125: 712-725, 2019.
139. Alhosin M, Razvi SSI, Sheikh RA, Khan JA, Zamzami MA and Choudhry H: Thymoquinone and difluoromethylornithine (DFMO) synergistically induce apoptosis of human acute T lymphoblastic leukemia jurkat cells through the modulation of epigenetic pathways. Technol Cancer Res Treat 19: 1533033820947489, 2020.
140. Guan D, Factor D, Liu Y, Wang Z and Kao HY: The epigenetic regulator UHRF1 promotes ubiquitination-mediated degradation of the tumor-suppressor protein promyelocytic leukemia protein. Oncogene 32: 3819-3828, 2013.
141. Chow M, Gao L, MacManiman JD, Bicocca VT, Chang BH, Alumkal JJ and Tyner JW: Maintenance and pharmacologic targeting of ROR1 protein levels via UHRF1 in t(1;19) pre-B-ALL. Oncogene 37: 5221-5232, 2018.