Macrophage migration inhibitory factor: Exploring physiological roles and comparing health benefits against oncogenic and autoimmune risks (Review)

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Abstract. Macrophage migration inhibitory factor (MIF), a multifunctional cytokine that plays a central role in immune regulation and tissue homeostasis, is expressed by nearly all cell types in the body. Beyond its well-established pro-inflammatory functions, MIF also exerts protective effects in several physiological processes. MIF enhances immune defense by activating macrophages, promoting cytokine release and supporting efficient antigen presentation. Additionally, MIF contributes to tissue repair, neuroprotection, cardiac function and metabolic regulation, facilitating epithelial healing, maintaining redox balance and modulating insulin secretion. MIF signals through multiple receptors, including CD74, CD44, CXC motif chemokine receptor (CXCR)2, CXCR4 and CXCR7, enabling it to act across a wide range of cell types. This complex signaling network allows MIF to function as both a mediator of homeostasis and a driver of pathology, depending on the biological context. Elevated MIF levels and polymorphisms such as -794 CATT5-8 and -173G>C have been associated with increased susceptibility to and the severity of autoimmune disorders (such as systemic lupus erythematosus, multiple sclerosis and rheumatoid arthritis), cancer (such as breast, lung and colorectal cancer) and other inflammatory diseases. MIF promotes tumor progression, immune evasion and glucocorticoid resistance, positioning it as a potential biomarker and therapeutic target. Therapeutic strategies targeting MIF, such as small-molecule inhibitors, receptor antagonists and proteolysis-targeting chimeras, have shown promise in preclinical studies. However, translating these strategies into clinical therapies requires a deeper understanding of the tissue-specific functions of MIF and the long-term consequences of its modulation. Future research should focus on elucidating the mechanisms underlying the dual roles of MIF in health and disease, the impact of genetic variations and the development of targeted interventions that preserve its protective functions while minimizing its pathogenic potential. Such insights will be essential for advancing MIF-based therapies in precision medicine.

Contents

1. Introduction

Macrophage migration inhibitory factor (MIF) was first identified by Bloom and Bennett (1) in 1966 as a soluble factor produced by sensitized lymphocytes in response to specific antigens, inhibiting macrophage migration *in vitro*. They proposed three potential mechanisms for this inhibition, including the release of a pharmacological agent or an antibody-like substance, laying the foundation for understanding the role of MIF in immune responses (1,2).

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The cloning of human MIF cDNA in 1989 provided the first clear insights into its biological activities (3). By 1994, bioactive MIF protein and neutralizing antibodies were being produced, revealing macrophages as both a source and target of MIF and underscoring its role in systemic inflammation (4). In 1995, MIF was identified as a glucocorticoid-induced modulator of cytokine production that balances pro- and anti-inflammatory responses (5). Structural experiments in 1996 revealed the unique ligand-receptor interactions of MIF, distinguishing it from other cytokines (6).

Between 1996 and 2003, the tautomerase activity of MIF and its involvement in infectious diseases, autoimmunity, cancer and atherogenesis were established (7-9). In 1998, the discovery of a CXXC motif in MIF explained its thiol-protein oxidoreductase activity, while its enzymatic role in detoxifying oxidized catecholamines suggested a protective function in neural tissue (10,11). The association of MIF with rheumatoid arthritis (RA) also emerged, with its inhibition proposed as a potential therapeutic strategy (12,13).

In 2003, the circadian rhythm of MIF was found to counteract the immunosuppressive effects of cortisol, and CD74 was identified as its high-affinity receptor, elucidating its molecular interactions (14,15). By 2006, CD44 was shown to mediate MIF-induced signaling via ERK1/2 phosphorylation (16) and in 2007, MIF was revealed as a non-cognate ligand for CXC motif chemokine receptors (CXCRs), further expanding its role in immune regulation (17).

A subsequent study in 2012 linked MIF to autophagy under stress conditions, and in 2021, MIF was proposed to function as a 3' nuclease, facilitating cancer cell evasion of replication stress (18,19). These discoveries collectively underscore the multifaceted roles of MIF in inflammation, immunity and disease, making it a critical focus of ongoing therapeutic research. A timeline illustrating this decades-long journey in MIF research is presented in Fig. 1.

2. Localization and secretion

Cellular localization of MIF. MIF is primarily localized within the cytoplasmic vesicles of cells across most tissues, although it can also be detected in the nucleus (20). This dual localization enables the rapid secretion of MIF without the need for new protein synthesis. When MIF is required for secretion, an N-terminal signal sequence facilitates its translocation into the endoplasmic reticulum and Golgi apparatus for conventional processing. Additionally, previous studies have identified exosomes as an alternative secretory pathway, further expanding our understanding of the mechanisms involved in MIF release (20-22). The expression and secretion of MIF are enhanced by diverse stimuli, including pathogen-associated molecules such as lipopolysaccharide (LPS) and exotoxins, inflammatory mediators such as TNF-α and thrombin, metabolic factors such as glucose and insulin, and environmental stressors such as hypoxia and ultraviolet B irradiation. These findings demonstrate the complex regulation of MIF under various physiological and pathological conditions (20-22).

Mechanisms of MIF secretion. In addition to the aforementioned canonical pathway, MIF can also be secreted via a non-canonical route; however, the precise molecular mechanisms underlying this alternative pathway remain incompletely understood (23). Current research suggests that MIF release is mediated through programmed cell death pathways, including necrosis, necroptosis and NLRP3 inflammasome-dependent pyroptosis (20-22). Additionally, components of the vesicular transport system, such as the general vesicular transport factor p115 and the ATP-binding cassette transporter ABCA1, appear to participate in MIF secretion. Once released, MIF can act in an autocrine manner on the producing cell or in a paracrine fashion on neighboring cells, amplifying its biological effects (20-22).

Expression in different tissues. Originally characterized as a T cell-derived cytokine (1,2) MIF is now known to be widely expressed across various cell types and tissues. As detailed in Table I, MIF is produced by immune cells (such monocytes, macrophages and T lymphocytes), structural cells (such as epithelial, endothelial and smooth muscle cells) and specialized cells in the nervous system and pituitary gland. MIF is also detectable in circulating blood components, including white blood cells, plasma, red blood cells and platelets (24-28). Tissue-specific expression pattern analysis has revealed that MIF is present in the basal layer of the epidermis and in keratinocytes, where its levels increase during inflammatory skin conditions (29). Pancreatic islet β-cells also produce MIF in a glucose-dependent manner, while insulin-target cells such as skeletal muscle and adipose tissue exhibit variable secretion rates depending on anatomical location (30).

Pathological significance. The pathological consequences of MIF hypersecretion are well documented (16,25,29). For instance, in vitiligo, elevated serum MIF is correlated with disease severity and duration, promoting autoimmune-mediated melanocyte destruction through macrophage recruitment and sustained inflammation (29). Similarly, in gastric cancer, MIF expression progressively increases from gastritis to malignancy, contributing to tumorigenesis via mechanisms including angiogenesis and immune evasion (25). Beyond its role in disease, MIF participates in physiological inflammatory responses by upregulating adhesion molecules (such as E-selectin, intercellular adhesion molecule-1 and Vascular Cell Adhesion Molecule-1) and chemokines (such as IL-8 and MCP-1), thereby enhancing leukocyte recruitment to sites of inflammation (22,31-34). Notably, in healthy individuals, serum MIF concentrations typically range from 0.2 to 8.3 ng/ml. However, these levels are significantly elevated in the aforementioned diseases, as well as in a wide range of other pathological conditions, including autoimmune disorders, chronic inflammatory diseases and diverse malignancies, as illustrated in Table II (16,25,29,35-46).

3. Genetics

The first reports describing the sequence of both MIF cDNA and its corresponding gene emerged in the early 1990s. The D-dopachrome tautomerase (D-DT) gene is closely related to the MIF gene and is considered to have originated through the duplication of a common ancestral gene. In humans, there is only one MIF gene, which is located on chromosome 22 (22q11.23). This gene consists of three exons measuring 107,

Table I. MIF expression in different cell types.

Cell type	Description	(Refs.)
Endothelial cells	MIF secreted by endothelial cells during inflammation plays a key paracrine role in relaxing adjacent pericytes, thereby facilitating neutrophil extravasation through the microvascular barrier.	(28)
HHSECs	MIF released by HHSECs acts as a central paracrine signal promoting colorectal cancer cell chemotaxis, proliferation, invasion and metastasis in the liver. MIF contributes to the formation of a prometastatic niche and represents a potential therapeutic target.	(26)
HUVECs	MIF is secreted in response to LPS stimulation, with its expression varying depending on both the duration and dose of exposure. Additionally, the expression of MIF is upregulated following TNFα stimulation.	(24,27)
Gastric epithelial cells	MIF expression progressively increases from inflammation to metaplasia and gastric cancer. MIF promotes epithelial proliferation, sustains chronic inflammation and may function as a biomarker and therapeutic target in gastric carcinogenesis.	(25)

HHSECs, human hepatic sinusoidal endothelial cells; HUVECs, human umbilical vein endothelial cells; LPS, lipopolysaccharide; TNFα, tumor necrosis factor α.

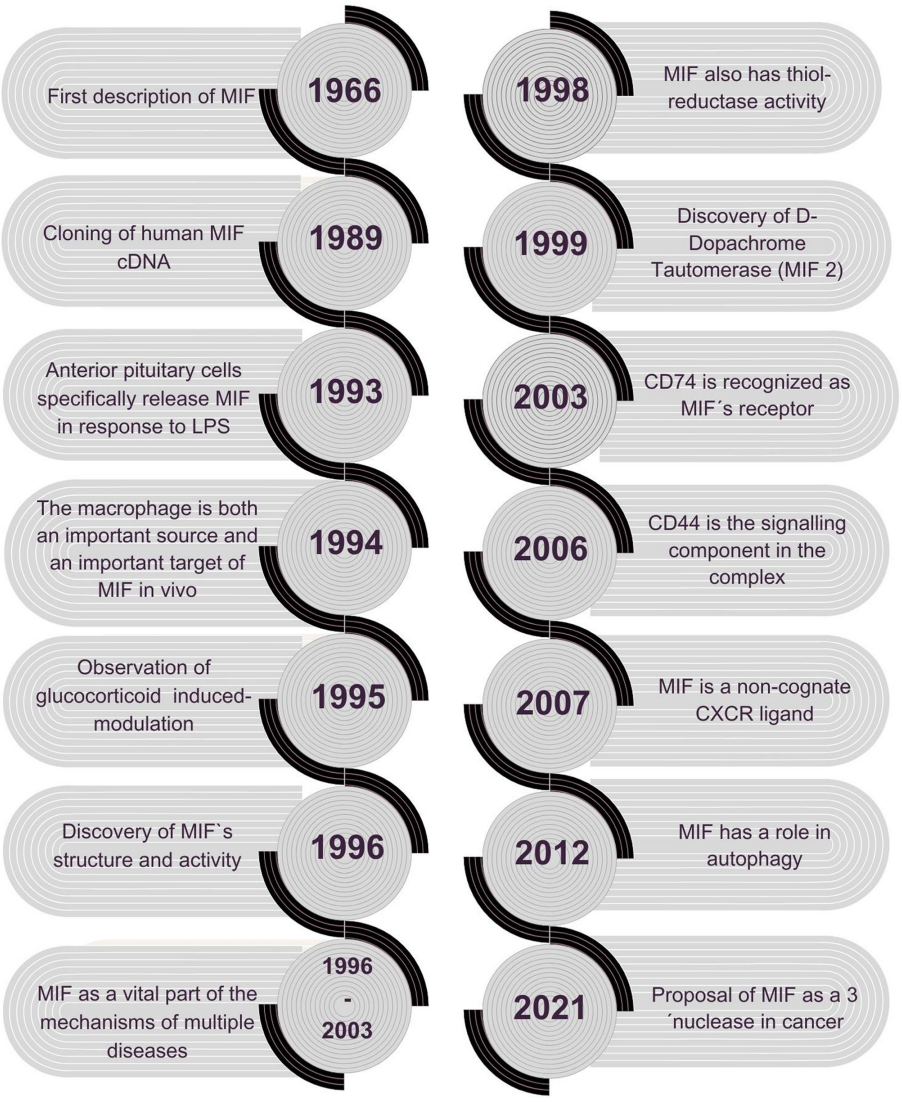

Figure 1. Although MIF was discovered nearly 60 years ago, our understanding of its role in a wide range of biological processes has significantly advanced only in recent decades. MIF, macrophage migration inhibitory factor; LPS, lipopolysaccharide.

Table II. MIF expression in certain pathological conditions.

A, Autoimmunity

Pathological condition	MIF serum concentration (ng/ml)	(Refs.)
Polymyositis	50[a]	(35)
Vitiligo	32.96[a]	(29)
Alopecia areata	3.56-11.10[c]	(36)
Rheumatoid arthritis	21.7±11.2[a]	(37,38)
Systemic lupus erythematosus	20±11[a]	(38)
Sjögren's syndrome	29.8[b]	(39)

B, Cancer

Pathological condition	MIF serum concentration (ng/ml)	(Refs.)
Esophageal squamous cell carcinoma	100[a]	(40)
Gastric cancer	9.7[b]	(25)
Localized breast cancer	0.1-21.5[c]	(41)
Metastasized breast cancer	0.4-50.0[c]	(41)

C, Infection

Pathological condition	MIF serum concentration (ng/ml)	(Refs.)
Dengue shock syndrome	102[a]	(16)
Pulmonary tuberculosis	19.84[a]	(42)
Periodontitis	71.8[a]	(43)
Severe sepsis	103.7[a]	(44)
Glomerulonephritis	15.2[a]	(45)

D, Other

Pathological condition	MIF serum concentration (ng/ml)	(Refs.)
Kawasaki disease	113.06[b]	(46)

[a]Mean value. [b]Median value. [c]Range (min-max).

172 and 66 base pairs, and two introns measuring 188 and 94 base pairs, respectively. Both the exonic structure and the DNA sequence of MIF are highly conserved across species. As a result, MIF displays the highest degree of amino acid sequence homology among human-mouse cytokine pairs. MIF contains CpG islands, which contribute to its consistent expression as a single ~0.8 kb mRNA transcript (3). CpG islands are regions rich in cytosine and guanine nucleotides linked by phosphate bonds, typically located near gene promoters, which play a critical role in transcriptional regulation by serving as binding sites for transcription factors and influencing chromatin structure. In the case of MIF, the presence of CpG islands in its promoter region helps maintain an open chromatin configuration, promoting transcriptional activity and ensuring stable, constitutive gene expression under both physiological and pathological conditions (22,31-34).

The regulation of MIF gene expression is influenced by two well-characterized polymorphic sites located in the promoter region. The first consists of a variable number of CATT repeats at position-794, typically ranging from 5 to 8 copies. The second is a single nucleotide polymorphism at position-173 (G>C). The presence of >5 CATT repeats and the-173C allele has been associated with increased susceptibility to, and the severity of, various inflammatory and autoimmune diseases such as RA and systemic lupus erythematosus (SLE) (32). These polymorphisms have also been associated with an elevated risk of developing prostate and gastric cancer (22,31-34).

4. Structure and enzymatic activities

MIF has a homotrimer structure composed of three identical subunits. Each monomer has an approximate molecular weight of 12.5 kDa and contains 114 amino acids. The assembled trimer has a three-fold rotational symmetry with a solvent-accessible channel at its core. Each monomer comprises two antiparallel α-helices and a four-stranded β-sheet. Based on structural experiments, the central channel may serve as a potential binding site for small molecules. Initially, the biological function of this binding capacity was hypothesized to involve ligands such as glutathione, gangliosides or dopachrome (47).

As aforementioned, MIF possesses tautomerase activity, specifically catalyzing the conversion of D-dopachrome to 5,6-dihydroxyindole-2-carboxylic acid (11). Further enzymatic analyses have demonstrated that MIF also acts as a phenylpyruvate tautomerase, with phenylpyruvate and *p*-hydroxyphenylpyruvate as substrates, and as a thiol-protein oxidoreductase (10). These multifaceted catalytic functions have led to its classification as a cytozyme, reflecting its dual role as a cytokine and enzyme. Research by Matsunaga *et al* (11) revealed that MIF can catalyze the conversion of 3,4-hydroxyphenyl amine chrome and norepinephrine chrome, both toxic quinone derivatives of catecholamine neurotransmitters, into indole dihydroxy derivatives. These products may serve as precursors for neuromelanin, suggesting that MIF plays a protective role in neural tissue by detoxifying reactive catecholamine breakdown products (48). Structural experiments have shown that the N-terminal Pro1 is essential for catalytic function; insertion of an Ala between Pro1 and Met2, or replacement of Pro1 with Ser or Gly, abolishes tautomerase activity (11).

The enzymatic activity of MIF has been shown to be essential for optimal signaling in inflammatory and tumorigenic pathways. Additionally, the C-terminal domain has been implicated not only in enzymatic regulation but also in maintaining the tertiary structure of the protein (48). Consequently, the C-terminal region has emerged as a potential target for allosteric inhibition of enzymatic function.

Table III. Roles of MIF/CD74 in physiological processes.

Function	Mechanism	(Refs.)
Regulation of cell survival	Involves Syk tyrosine kinase and the PI3K/Akt pathway activation, leading to intramembrane cleavage of CD74 and release of the CD74-ICD.	(51-53)
Control of cell metabolism	In macrophages, CD74-ICD is phosphorylated via protein kinase A, followed by CD44 recruitment and phosphorylation, activating Src-family kinases and downstream ERK1/2.	(54)
Cell adhesion	JAB1, an intracellular MIF-binding protein, regulates the sustained phase of MIF-induced ERK phosphorylation.	(55)
Hypoxia	MIF regulates hypoxia-induced HIF1α expression via CD74, forming an autocrine positive-feedback loop.	(56)
Osteoclastogenesis	MIF/CD74/CD44 signaling activates Lyn phosphorylation, which downregulates RANKL- induced Gab2/JNK-1/c-Jun and Syk/PLCγ pathway, suppressing NFATc1 activation.	(57)

CD74-ICD, CD74 intracellular domain; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; JAB1, jun activation domain-binding protein 1; HIF1α, hypoxia-inducible factor 1-α; RANKL, receptor activator of nuclear factor κ-β ligand; Gab2, GRB2-associated-binding protein 2; JNK, c-jun N-terminal kinase; NFATc1, nuclear factor of activated T cells, cytoplasmic 1; PLCγ, phospholipase Cγ.

Among small-molecule inhibitors, 4-iodo-6-phenylpyrimidine (4-IPP) has been described as a 'suicide substrate' irreversibly inhibiting the tautomerase activity of MIF; it has demonstrated greater potency than ISO-1, with 4-IPP being associated with improved survival outcomes in murine models of sepsis. This specificity suggests that inhibition of MIF's enzymatic activity may preferentially affect tumorigenic processes while sparing physiological inflammatory responses (6,11,48,49).

5. Receptors and signaling pathways

CD74

Structure and expression. CD74 was the first non-polymorphic protein shown to associate with polymorphic major histocompatibility complex (MHC) class II molecules (50). Structurally, it comprises an N-terminal cytosolic tail, a transmembrane domain and a luminal C-terminal domain. The CD74 gene, located on chromosome 5, encodes four isoforms (50). CD74 is primarily expressed by professional antigen-presenting cells such as dendritic cells, B cells and macrophages, but it is also found in endothelial, epithelial and some mesenchymal cells (21).

Function and interaction with MIF. Within the endoplasmic reticulum, CD74 assembles into trimers and functions as a chaperone for MHC class II molecules, which is why it is also known as the 'class II invariant chain' (50). CD74 is produced in excess to ensure availability for MIF binding, independent of MHC II expression. Leng *et al* (15) reported that CD74, synthesized using a coupled transcription-translation reticulocyte lysate system, binds to MIF *in vitro*. Notably, a 40-amino acid segment within the extracellular domain of CD74 (residues 109-149) was identified as essential for mediating this interaction. Each CD74 trimer is capable of binding three MIF molecules. D-DT, a homolog of MIF, also binds CD74, albeit with faster association and dissociation kinetics than MIF (34).

Some parasites, including *Plasmodium, Entamoeba, Toxoplasma* and *Leishmania*, express MIF homologs that may exploit the MIF-CD74 interaction to evade host immune responses (50). MIF binds to the CD74-CD44 receptor complex, mediating inflammatory cell recruitment through downstream CXCR2 and CXCR4 signaling. This MIF-receptor interaction also activates the anti-apoptotic gene Bcl-xL, enhancing B cell survival; however, the precise mechanisms remain under investigation (20,21).

Additionally, MIF, through its interaction with the CD74 receptor, plays a pivotal role in the regulation of various physiological processes. MIF facilitates cell survival by activating Syk tyrosine kinase and the PI3K/Akt signaling pathway, culminating in the intramembrane cleavage of CD74 and the release of its intracellular domain (CD74-ICD) (51-53). In macrophages, phosphorylation of CD74-ICD by protein kinase A, followed by CD44 recruitment, leads to the activation of Src-family kinases and downstream ERK1/2 signaling, thereby modulating cellular metabolism (54). MIF also influences cell adhesion via the intracellular MIF-binding protein, Jun activation domain-binding protein 1 (JAB1), which sustains MIF-induced ERK phosphorylation (55). Under hypoxic conditions, MIF enhances hypoxia-inducible factor 1α (HIF1α) expression through a CD74-dependent autocrine positive-feedback mechanism (56). Furthermore, MIF/CD74/CD44 signaling exerts an inhibitory effect on osteoclastogenesis by inducing Lyn phosphorylation, which attenuates the receptor activator of NF-κB ligand-mediated Gab2/c-Jun N-terminal kinase (JNK)-1/c-Jun and Syk/phospholipase Cγ signaling pathways, ultimately suppressing the activation of nuclear factor of activated T cells 1 (57). These mechanisms are listed in Table III.

CD74 in inflammation and signaling. CD74 plays an important role in tissue repair associated with inflammation, particularly in conditions such as inflammatory bowel disease, where it protects epithelial cells from oxidative stress in

Table IV. CD74-mediated tissue repair.

Organ	Mechanism	(Refs.)
Intestine	MIF-CD74 signaling activates Akt and ERK pathways, promoting crypt cell proliferation and facilitating epithelial barrier restoration after injury.	(50)
Nervous system	MIF-CD74 signaling supports the generation of Schwann cells and neural stem cells, contributing to nerve regeneration.	(60)
Liver	MIF-CD74 interaction promotes AMPK activation in hepatocytes, offering protection against fatty liver disease.	(61)
Skin	CD74 expression increases during cutaneous wound healing, indicating a role in epithelial regeneration.	(62)
Lung	MIF-CD74 signaling promotes restoration of the alveolar epithelial barrier after injury via Akt activation.	(28)
Heart	CD74 activation promotes cardiomyocyte survival through AMPK and provides protection against ischemic injury.	(58,63)
Kidney	CD74 signaling activates SLPI, promoting tubular cell proliferation and recovery of renal function after acute kidney injury.	(64,65)

CD74, cluster of differentiation 74; AMPK, AMP-activated protein kinase; SLPI, secretory leukocyte protease inhibitor; ERK, extracellular signal-regulated kinase.

experimental models (50). MIF binding to CD74 activates the ERK1/2 pathway, a member of the mitogen-activated protein kinase (MAPK) family, which regulates cell proliferation, differentiation and stress responses (55,58). This interaction also enhances arachidonic acid metabolism, prostaglandin synthesis and Toll-like receptor expression via Ets-family transcription factors (59). Table IV illustrates additional downstream pathways activated by MIF-CD74 binding include PI3K/Akt, NF-κB and AMP-activated protein kinase (AMPK), all of which contribute to cellular survival, proliferation and metabolic regulation (28,50,58,60-65).

Regulation of CD74. CD74 expression is upregulated by interferon-γ (IFN-γ), a key mediator of both innate and adaptive immunity (50). CD74 also exists in a soluble form, generated through proteolytic shedding of its ectodomain, which reduces the availability of the membrane-bound receptor for ligand interaction (50). Interactions between MIF and CD74 are further modulated by proteins such as ribosomal protein S19 and JAB1, both of which act as competitive inhibitors of MIF binding (50).

CD44

Structure and function. CD44 is a key co-receptor in MIF signaling and plays important roles in cellular adhesion, migration, lymphocyte activation and angiogenesis. CD44 primarily functions through extracellular matrix (ECM) adhesion mechanisms (21,66). The CD44 gene, located on chromosome 11p13, contains 19 exons in humans, while mice possess an additional variant exon (v1). CD44 is broadly expressed in lymphocytes, fibroblasts and smooth muscle cells.

CD44 in disease and MIF signaling. CD44 has been studied in cancer due to the involvement of its splice variants in tumor progression (67). The extracellular domain of CD44 can bind to MIF, thereby modulating downstream signaling cascades, as illustrated in Fig. 2 (67). The splice variants v3 and v6 of CD44 are particularly elevated in T cells from patients with SLE and in fibroblast-like synoviocytes from patients with RA, contributing to enhanced invasiveness and inflammation (22). For MIF signal transduction to occur, CD74 and CD44 must form a cis-complex on the plasma membrane (68). This complex triggers the activation of Src-family tyrosine kinases and subsequent signaling through the PI3K/Akt and AMPK pathways (21). Binding of D-DT to the CD74/CD44 complex can also activate the ERK1/2 pathway (67). Beyond inflammation and cancer, CD44 has been implicated in metabolic diseases such as insulin resistance, likely due to its interactions with hyaluronan and modulation of MIF-related signaling (67).

CXCRs: CXCR2, CXCR4 and CXCR7. MIF directly binds to three CXCRs, CXCR2, CXCR4 and CXCR7, each with distinct expression profiles. CXCR2 is predominantly expressed on neutrophils and endothelial cells, while CXCR4 and CXCR7 have broader distributions, including hematopoietic, endothelial and neuronal cells (22). Although MIF shares low sequence homology with natural ligands, such as CXC motif chemokine ligand (CXCL8) and SDF-1 (CXCL12), it contains specific motifs that enable receptor binding upon protein folding. Notably, D-DT does not bind CXCR2 (34). The prototypical function of MIF, inhibition of macrophage migration, is mediated by CD74-dependent recruitment of inflammatory cells through CXCR2 and CXCR4 (22,32,33,43,50). MIF also promotes monocyte adhesion and transendothelial migration, involving chemokines such as CXCL1 and CXCL8 (33).

CXCR-mediated signaling and immune modulation. MIF recruits myeloid-derived suppressor cells (MDSCs) via CXCL2-CXCR2 signaling, activating the MAPK and NF-κB pathways (31). However, MIF does not always mimic natural chemokine signaling. For example, it fails to activate ERK1/2 in platelets that lack CD74, indicating that CD74 is essential for CXCR2/4-mediated MIF signaling (21). Neutralization

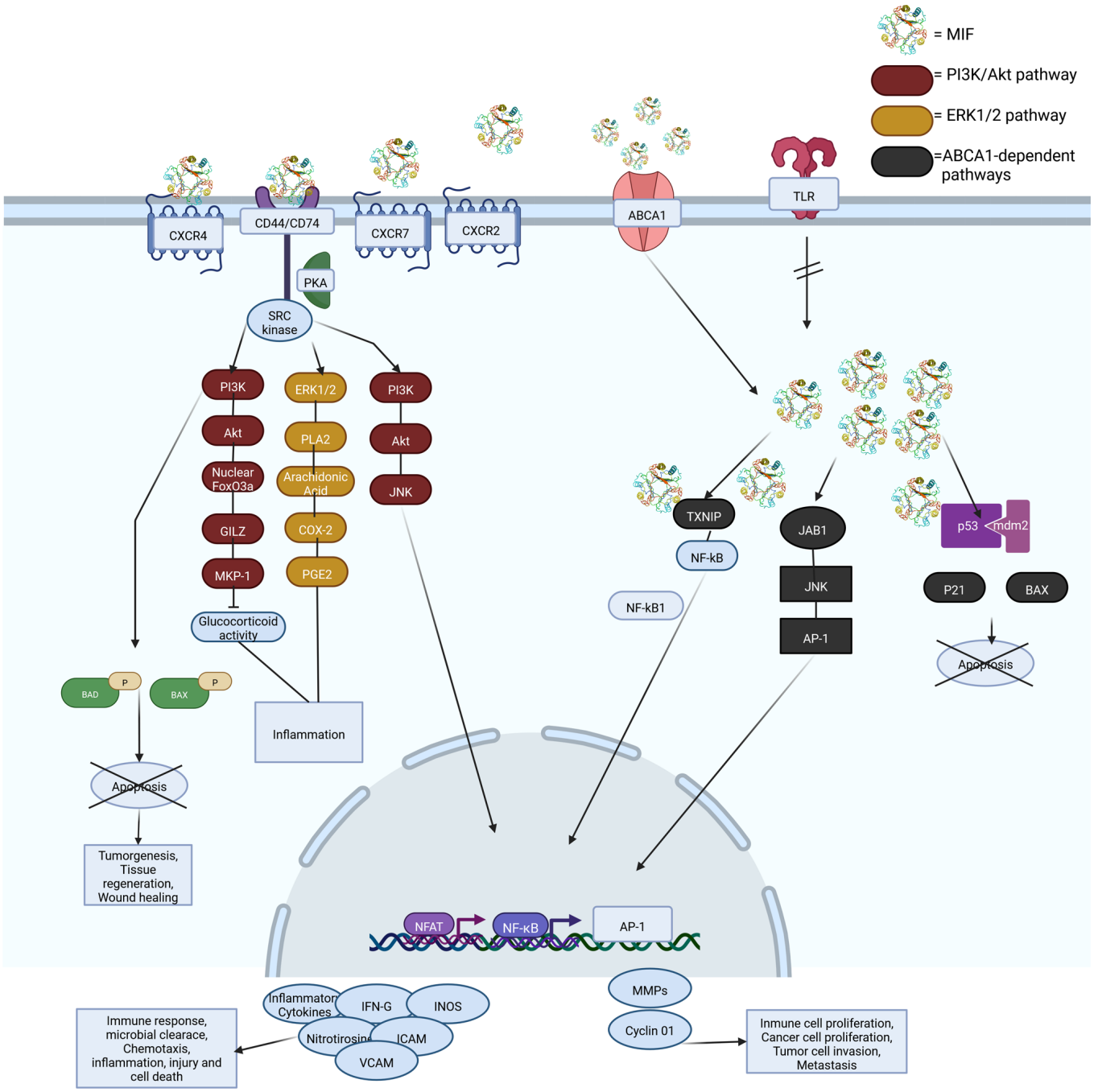

Figure 2. MIF signaling pathway illustrates how this multifunctional molecule links immune response, inflammation and oncogenic processes. CXCR2/4/7, C-X-C motif chemokine receptor 2/4/7; TLR, Toll-like receptor; ABCA1, ATP binding cassette subfamily A member 1; ERK1/2, extracellular signal-regulated kinase 1/2; PLA2, phospholipase A2; FoxO3a, forkhead box O3a; JNK, c-Jun N-terminal kinase; GILZ, glucocorticoid-induced leucine zipper; COX2, cyclooxygenase-2; MKP-1, MAP kinase phosphatase 1; PGE2, prostaglandin E2; BAD, Bcl-2-associated agonist of cell death; BAX, Bcl-2-associated X protein; NFAT, nuclear factor of activated T cells; AP-1, activator protein 1; IFN-γ, interferon γ; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; iNOS, inducible nitric oxide synthase; MMPs, matrix metalloproteinases; TXNIP, thioredoxin-interacting protein; Mdm2, mouse double minute 2 homolog.

of CD74 abrogates signal transduction, reinforcing its critical role (21). When MIF binds to CD74 in complex with CXCR2 or CXCR4, it activates ERK1/2 and Akt through Gαi-coupled signaling. This complex may undergo internalization, potentially exposing these receptors on the surface of various tumors suggests that MIF-mediated effects are highly context-dependent (68).

CXCR7-specific roles. CXCR7 differs functionally from CXCR2 and CXCR4. Instead of initiating transient G-protein-coupled signaling, it shifts ERK1/2 activation toward a sustained β-arrestin-2-mediated pathway. Although CXCR7 was initially considered an atypical chemokine receptor, it is now recognized as a direct non-canonical receptor for MIF. MIF binding to CXCR7 can occur independently or in complex with CD74 and/or CXCR4, potentially modulating β-arrestin signaling and influencing cell migration and survival (20,21). CXCR7 has also been implicated in B cell trafficking and shown to activate ZAP-70, suggesting

Table V. Beneficial effects of MIF in health.

Effect	Description	(Refs.)
Regulation of the immune response and microbial clearance	Enhances macrophage activation, promotes cytokine production (such as TNF-α, IFN-γ, IL-1βand IL-6), and facilitates microbial clearance, antigen presentation and parasitic recognition.	(69-71)
Renal protection	Protection against renal ischemia-reperfusion injury, particularly after cardiac surgery, through interactions between MIF and soluble CD74.	(65)
Cardioprotection	Reduces myocardial oxidative stress and apoptosis, maintains redox balance and activates AMPK/ERK cardioprotective pathways via CD74. These effects are linked to S-nitrosylation at cysteine 81.	(10,63,72-74)
Neuroprotection	Inhibits inflammation and apoptosis in Alzheimer's and Parkinson's disease, stimulates autophagy, rescues neurons from SOD1-induced death and enhances cognitive function by activating survival pathways.	(11,60,75-77)
Maintenance of immune-privileged sites	Prevents NK cell-mediated cytolysis by inhibiting perforin release, thereby preserving immune privilege in sensitive tissues.	(78-79)
Regeneration of cells and wound healing	Promotes migration of fibroblasts and keratinocytes, granulation tissue formation, angiogenesis and regeneration of corneal, epithelial and nerve tissues; supports Schwann cell survival and suppresses p53. Akt/ERK activation is CD74-dependent.	(80-82)
Regulation of insulin secretion	Enhances insulin secretion via autocrine/paracrine signaling, regulates PDX-1 expression for insulin gene transcription and increases glycolytic flux through the 6-phosphofructo-2-kinase activity.	(30,83,84)

CD74, cluster of differentiation 74; TNF-α, tumor necrosis factor α; IFN-γ, interferon γ; IL, interleukin; AMPK, AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; SOD1, superoxide dismutase 1; NK, natural killer; PDX-1, pancreatic and duodenal homeobox 1.

broader roles in immune regulation. These findings indicate that MIF may exert context-dependent effects through its interaction with CXCR7, distinct from classical chemokine pathways (21,22).

6. Roles of MIF in health

As aforementioned, MIF is a multifunctional protein that plays a crucial role in maintaining physiological homeostasis. MIF regulates immune responses by enhancing macrophage activity, promoting the production of pro-inflammatory cytokines, including TNF-α, IFN-γ, IL-1β, IL-2, IL-6 and IL-8, and facilitating pathogen clearance through the induction of nitric oxide (NO), cyclooxygenase-2 (COX-2) and efficient antigen presentation (69-71). MIF also modulates cellular proliferation and differentiation by activating key signaling pathways such as p44/42 ERK MAPK and cytosolic phospholipase A2. These pathways drive the production of inflammatory mediators (such as prostaglandins and arachidonic acid) and activate JNK/stress-activated protein kinase, which further amplify TNF-α signaling (22).

The broad physiological functions of MIF, detailed in Table V, also include organ protection. For example, MIF attenuates renal ischemia-reperfusion injury through its interaction with CD74 (59) and maintains cardiac redox homeostasis via S-nitrosylation at Cys81, reducing oxidative stress and apoptosis while activating the AMPK and ERK pathways (10,63,72-74). MIF also exerts neuroprotective effects, including the suppression of inflammation and apoptosis in Alzheimer's and Parkinson's disease, stimulation of autophagy and the rescue of neurons from superoxide dismutase 1-induced death (11,60,75-77). MIF contributes to tissue repair by promoting fibroblast and keratinocyte recruitment, enhancing angiogenesis and accelerating nerve regeneration through p53 suppression (78,79). In corneal and intestinal wounds, MIF activates Akt/ERK signaling to promote epithelial healing (80-82) Moreover, MIF plays a role in metabolic regulation, modulating insulin secretion via regulation of pancreatic and duodenal homeobox-1 and increased production of fructose-2,6-bisphosphate (30,83,84). This range of functions underscores the therapeutic potential of MIF in a variety of medical fields, including immunology, neurology, cardiology and metabolic disorders.

7. Roles of MIF in disease

MIF is widely recognized as a pivotal mediator in the pathogenesis of various inflammatory and immune-related diseases. MIF plays a central role in multiple pathological conditions, ranging from acute systemic inflammation to chronic autoimmune disorders and malignancies. For instance, in sepsis, MIF contributes to excessive and dysregulated inflammatory responses, exacerbating disease severity (85). In RA, MIF has been implicated in joint inflammation, synovial hyperplasia and cartilage degradation (86). MIF also plays a pathogenic role in diabetes mellitus, where it contributes to insulin resistance and pancreatic β-cell dysfunction (87). In the context of cancer, MIF promotes tumor progression, angiogenesis

and immune evasion, underscoring its potential as a therapeutic target in solid tumors and other malignancies (33). The involvement of MIF in acute respiratory distress syndrome highlights its contribution to pulmonary inflammation and epithelial injury (88). Similarly, in multiple sclerosis (MS), MIF has been linked to neuroinflammation and disease exacerbation, further emphasizing its immunomodulatory role in neurological autoimmune disorders (89). MIF is also implicated in systemic autoimmune diseases such as SLE (90) and psoriasis (91), where it regulates immune cell activation and the secretion of pro-inflammatory cytokines. In dermatological conditions such as alopecia areata (AA), MIF may influence immune-mediated hair follicle destruction (92). In infectious diseases such as dengue, MIF contributes to the amplification of the inflammatory response and is associated with increased disease severity (22,93).

The pathogenic effects of MIF are mediated through several key mechanisms. One of the primary pathways involves the induction of inflammatory mediators, including TNF-α, NO, interleukins (such as IL-1, IL-6 and IL-8) and COX, all central components of the inflammatory cascade. MIF also modulates the response to LPS by acting in an autocrine manner to upregulate Toll-like receptor 4 and its co-receptor myeloid differentiation factor 2, thereby intensifying the immune response to bacterial endotoxins (22). Collectively, these findings suggest that MIF serves as a crucial link between innate immunity and chronic inflammation, reinforcing its potential as a therapeutic target in the treatment of diseases characterized by excessive immune activation and inflammatory damage.

MIF and cancer

Tumor microenvironment (TME). The TME refers to the cellular and molecular milieu surrounding a tumor within the host's biological system. The TME is composed of vascular structures, immune and inflammatory cells (often bone marrow-derived), fibroblasts, ECM and the dynamic interactions among these components within the lymphatic and circulatory systems (94,95). The TME contributes significantly to tumor heterogeneity, progression and drug resistance. Non-malignant cells within the TME often play pro-tumorigenic roles throughout carcinogenesis, supporting uncontrolled cellular proliferation (95). For tumor development and metastasis to occur, cancer cells must acquire the ability to migrate, degrade the ECM, survive in circulation and colonize distant tissues. According to Mantovani *et al* (96), tumor-associated macrophages (TAMs) are the most abundant immune cells in the TME, supporting tumor progression by facilitating intravasation and protecting tumor cells from immune attack (94,96).

The TME is typically hypoxic, promoting the expression of MIF and other pro-inflammatory cytokines (96) (Fig. 3). Chronic inflammation, particularly mediated by MIF, promotes angiogenesis, resistance to apoptosis and tumor growth, which are hallmarks of malignancy (97-101). MIF contributes directly to these processes by activating key oncogenic pathways such as NF-κB, which acts as both a tumor initiator and promoter, and by inducing COX-2, which facilitates chemotherapy resistance. MIF also enhances STAT3 signaling, impairing dendritic cell function and allowing tumor immune evasion. Additionally, hypoxia and aberrant vasculature reinforce acidosis within the TME, which, in conjunction with MIF activity, drives malignant transformation and sustains the activation of HIF1α (Fig. 3) (96,102).

RAS family mutations are among the most frequent in human cancer (96). The RAS/RAF/MEK/ERK pathway triggers the production of pro-tumor cytokines and chemokines (96). The interaction between NF-κB and H1F1α leads to the upregulation of TNF-α and CXCR4, the latter being crucial for metastasis and a positive feedback loop for MIF expression (Fig. 3) (103). MIF, when secreted by cancer-associated fibroblasts (CAFs), promotes tumor cell activation by suppressing IFN signaling and inhibiting p53-dependent apoptosis (94); it also increases IL-6 production and amplifies tumor-promoting signals via the CXCR4/MIF/IL-6 loop (103). MIF also contributes to the polarization of macrophages toward a pro-inflammatory M1-like profile, yet its ultimate effect depends on the NF-κB mediated balance between pro- and antitumor functions (104). Thus, targeting MIF, its receptors (such as CD74 and CXCR4) and downstream mediators is necessary to disrupt the self-amplifying oncogenic loop (105). In parallel, strategies that re-educate tumor-promoting macrophages by modulating NF-κB could enhance antitumor immunity (Fig. 3) (94,106).

Quantifying MIF may have prognostic utility. A 2019 study identified elevated MIF and IL-17A levels as risk factors for breast cancer (BC) in the Mexican population (107). Novel therapies such as HSP90 inhibitors suppress MIF production in colorectal cancer (CRC) epithelial cells (108). Targeting MIF has shown promise in reducing the proliferation, angiogenesis and aggressiveness of cancer including triple-negative BC (TNBC), genitourinary cancer and pancreatic cancer (103,104,109,110). Additionally, combining autophagy inhibition with MIF targeting has been proposed for improved outcomes in TNBC (109).

BC. In BC, MIF contributes to carcinogenesis through upregulated pathways involved in proliferation, cell survival and growth. Among the molecular subtypes, high MIF levels are particularly associated with aggressive phenotypes, including the Luminal B, HER2-positive and TNBC subtypes (107). In TNBC, CD74 is strongly upregulated, leading to activation of the PI3K/Akt and MAPK pathways, which promote proliferation and survival. Co-expression of MIF and CD74 is also correlated with enhanced vascularity and elevated proangiogenic CXC chemokines, reinforcing the role of MIF in tumor aggressiveness and progression (63).

Beyond progression, MIF is linked to poor prognosis through its regulation of COX-2 expression and its facilitation of metastasis. Hypoxia upregulates MIF gene expression, further enhancing proliferation via PI3K/Akt activation. Moreover, HER2 upregulation induces heat-shock factor 1, which upregulates HSP90, a stabilizer of MIF (111). Collectively, these mechanisms contribute to uncontrolled tumor cell proliferation and highlight the value of MIF as a therapeutic and prognostic biomarker in BC.

Lung cancer. Similar to its role in BC, MIF significantly contributes to the progression of lung cancer, which remains the leading cause of cancer-related death in men and the second leading cause in women globally (112). Lung cancer is broadly classified into two main histological types: Non-small cell lung cancer (NSCLC) and small cell lung cancer (112). NSCLC

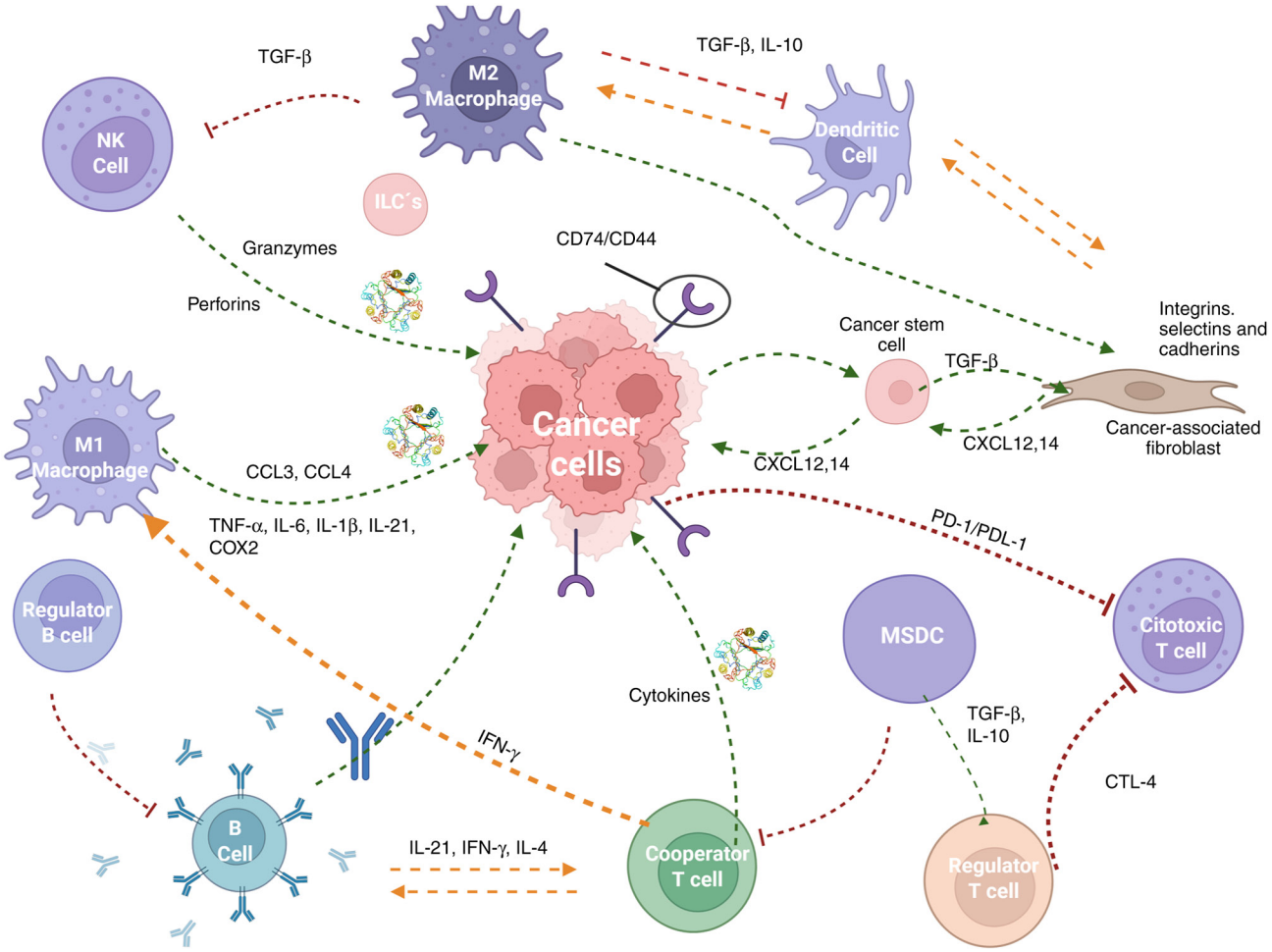

Figure 3. Numerous complex interactions occur between immune cells and cancer cells within the tumor microenvironment. This schematic provides a simplified overview of these interactions, with emphasis on the direct pro-tumorigenic effects of MIF. MIF contributes to immune evasion, chronic inflammation and tumor progression through its influence on cytokine production, immune cell polarization and signaling pathway activation. MIF, macrophage migration inhibitory factor; NK cell, natural killer cell; ILC, innate lymphoid cell; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; CTL, cytotoxic T lymphocyte; TGF-β, transforming growth factor-β; IL, interleukin; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase-2; PD-1, programmed death-1; PD-L1, programmed death ligand-1; CXCL12/14, C-X-C motif chemokine ligand 12/14.

represents 80-85% of all lung cancer cases, with over half of patients diagnosed at the advanced stages (112,113). MIF has a diagnostic and prognostic role by distinguishing normal lung tissues from NSCLC samples as well as correlating with elevated VEGF levels and increased microvessel density in tumors (114,115). Functionally, MIF promotes proliferation and inhibits apoptosis in NSCLC cell lines such as H460 and A549 (113).

At the molecular level, MIF is negatively regulated by microRNA-146a, a microRNA whose upregulation leads to reduced proliferation and increased apoptosis in lung cancer cells (115). Additionally, the CXCR4-upregulated MIF/IL-6 axis has been identified as a key driver of tumor-fibroblast crosstalk and NSCLC progression, suggesting therapeutic potential for CXCR4 inhibitors and MIF antagonists (103,113). MIF has also been associated with chemoresistance. Specifically, in cisplatin-resistant A549 and H460 cells, MIF expression is correlated with enhanced stemness and activation of the Src/CD155/MIF pathway, as well as upregulation of Notch1 and β-catenin. Inhibition of Src signaling has been shown to reduce these markers, supporting the strategy of combining Src inhibitors with chemotherapy in resistant NSCLC cases (116).

MIF also plays a key role in lung cancer metastasis, particularly to the brain, which occurs in up to 60% of NSCLC cases (117). Transcriptomic analysis by Liu *et al* (118) revealed high MIF expression in brain metastases. Additionally, blocking the MIF/CD74 axis enhances radiotherapy efficacy by shifting microglia toward the M1 antitumor phenotype, emphasizing the therapeutic value of targeting MIF in advanced NSCLC (117). In terms of therapeutic interventions, SCD-19, a small-molecule inhibitor that targets the tautomerase site of MIF, has demonstrated antitumor efficacy in a Lewis lung carcinoma model (119). Similarly, MD13, a PROTAC-based compound developed in China, induces MIF degradation and suppresses the MAPK pathway, inhibiting lung cancer cell growth (118).

CRC. In CRC, MIF contributes to inflammation-driven tumorigenesis and metastasis. The role of MIF in CRC parallels that observed in breast and lung cancer, reinforcing its broad relevance in oncology (120). One of the main mechanisms in the pathophysiology of this cancer involves the upregulation of CXCR4, a known MIF receptor, which enhances metastatic potential (121). Notably, CXCR4 is expressed in multiple cancer types, including breast, prostate and ovarian cancer,

as well as immune cells such as B and T lymphocytes (121). Through interaction with CXCL12 and MIF, CXCR4 activates a variety of signaling cascades, including G protein, ERK, JNK and JAK/STAT pathways, that support tumor growth and spread (121,122). The CXCR4/MIF axis has thus emerged as a significant driver of CRC metastasis and a promising therapeutic target (121,122).

Elevated MIF expression has been detected in patients with CRC and is correlated with advanced disease stages (123). Moreover, the MIF gene-173G/C polymorphism has been associated with increased MIF protein expression and higher CRC susceptibility. Within the colonic microenvironment, elevated MIF may also influence intestinal cell kinetics and amplify inflammatory responses, creating conditions conductive to malignant transformation (120). These findings collectively highlight the importance of further research into MIF as both a biomarker and a therapeutic target in CRC.

MIF and autoimmunity. Autoimmunity refers to a spectrum of diseases characterized by inappropriate immune responses against self-antigens, leading to tissue damage and chronic inflammation. These conditions arise from a dysregulated adaptive immune response directed at specific anatomical structures (124). In recent years, autoimmune diseases have been increasingly recognized as a global issue due to their chronic nature, substantial healthcare costs and high prevalence among working-age individuals; nearly 4% of the world's population is affected by one of >80 different autoimmune diseases. Notably, women are affected three times more frequently than men, prompting the National Institutes of Health to classify autoimmunity as a major health concern in women (124-127).

Autoimmune pathologies are heterogeneous in localization and may become systemic. Experimental evidence links the onset of autoimmunity to abnormalities in self-antigen presentation. A dysregulated innate immune response can also trigger autoimmunity (124). Despite the wide variety of conditions, all known autoimmune diseases are thought to follow a sequence of initiation, propagation and resolution. Clinical manifestations generally begin during the propagation phase, which is characterized by progressive inflammation and tissue damage (124,128).

It is hypothesized that multiple polymorphisms may be required to disrupt regulatory mechanisms or lower threshold for lymphocyte activation, and that epigenetics plays an important role in the development of such pathologies (128,129). As previously discussed, MIF serves a crucial role in inflammation by promoting mediators such as TNF-α, IL-1, IL-6, IL-8, IL-12, IFNγ, COX-2, NO and matrix metalloproteinases. MIF also affects lymphocyte activation by supporting macrophage survival and modulating their function through the inhibition of p53 (129). In B cells, MIF binding to CD74 triggers a signaling cascade that activates NF- κB/p65/RelA homodimer and its coactivator, TAFII105, which regulate the transcription of genes controlling lymphocyte survival and proliferation (124,129). These processes contribute to a self-sustaining inflammatory loop (128). Autoimmunity propagation is considered to be related to an increased ratio of effector to regulatory T cells (Tregs). Notably (and paradoxically), the inflamed skin of patients with psoriasis does not show such a shift in ratio; however, Tregs appear to function abnormally and produce increased amounts of IL-17 (128).

Infections remain a major suspected trigger of autoimmunity (125). A combination of microbial exposure and genetic defects may result in a breakdown of immune tolerance and homeostasis. Some bacterial strains have been shown to behave differently depending on the *in vivo* or *in vitro* context (130).

SLE. High-expression MIF alleles have been identified as a risk factor for the development of SLE (35,131-133). Recent studies have focused on the role of MIF in glomerulonephritis, especially lupus nephritis (LN) (35,131-133). The relationship between MIF and active LN appears to be complex and may involve interactions with other molecules such as adiponectin or resistin. The presence of MIF in urine may reflect not only renal excretion but also local production by tubular epithelial cells or infiltrating leukocytes (133,134). MIF is considered a contributor to both disease activity and the cumulative damage associated with SLE.

Zhou *et al* (35) demonstrated that CD74, the receptor for MIF, is upregulated in kidney epithelial cells and antigen-presenting cells, and that this upregulation can be induced by IL-6 or IFN-γ *in vitro*, highlighting its potential role in the autoimmune processes of SLE. SLE progression often requires increasing steroid treatment, which appears to be correlated with type I IFN activity. IFN can induce MIF expression in a time- and dose-dependent manner (132,135). Beltrán-Ramírez *et al* (135) proposed that MIF may increase the expression of P-glycoprotein by upregulating inflammatory cytokines such as TNF-α and IL-6. A broader cytokine panel, incorporating temporal expression, has been suggested for defining additional SLE subsets (136).

While ISO-1, the prototypical MIF inhibitor, is not considered a viable therapeutic option due to its low potency, alternative strategies have been explored for SLE (137). Artesunate (ART), an antimalarial drug, has been shown to counteract the effects of type I IFNs by inhibiting STAT1 phosphorylation, resulting in stabilization or even regression of atherosclerotic plaques in experimental models. These findings point to the IFN/MIF axis as a novel target in SLE-associated atherosclerosis (132). Additionally, IMMU-115, a MIF-targeted therapy, has shown acceptable toxicity and preliminary efficacy in patients with SLE; it reduces LN symptoms, with disease suppression maintained for up to 24 weeks following the initial dose (138).

Psoriatic arthritis (PsA). The role of MIF extends beyond SLE, playing a notable role in other autoimmune diseases such as PsA. PsA is a chronic inflammatory autoimmune disease marked by synovitis, enthesitis and aberrant bone remodeling, driven by dysregulated cytokine networks. Central to its pathogenesis is the IL-23/Th17 axis, with key cytokines such as IL-17, IL-22 and TNF-α playing pivotal roles in promoting inflammation, osteoclastogenesis and joint damage (139-143). Genetic predisposition, particularly involving HLA class I alleles such as HLA-B*27, and environmental triggers such as trauma and dysbiosis further contribute to the disease by amplifying aberrant immune responses (142,143).

MIF has emerged as a significant contributor to PsA pathogenesis. Secreted by macrophages, synovial fibroblasts and keratinocytes, MIF promotes synovial inflammation and joint destruction by enhancing the production of TNF-α, IL-17

and other cytokines, thereby sustaining the inflammatory loop and facilitating osteoclast (143,144). Compared with healthy controls, elevated serum and tissue levels of MIF have been documented in patients with PsA, supporting its involvement in disease pathology (140,145). Furthermore, genetic studies have implicated MIF promoter polymorphisms in the susceptibility to PsA. Notably, the-173 G>C variant, particularly the-173C allele and G/C genotype, has been associated with increased PsA risk in various populations, including Mexican Mestizos and British Caucasians (140,141,146) The CATT5/-173*C haplotype was also linked to psoriasis susceptibility in North Indian cohorts (145), reinforcing the relevance of MIF gene variants in psoriatic disease.

In psoriatic skin, MIF expression is upregulated in keratinocytes and endothelial cells, suggesting a broader role in the inflammatory processes of psoriatic disease beyond the joints (144). Experimental models further support this notion: MIF-deficient mice exhibit reduced keratinocyte hyperproliferation and inflammatory cell infiltration in psoriasiform dermatitis, indicating a potential mechanistic role for MIF in skin pathology (91). Despite these insights, additional studies are needed to fully delineate the multifaceted role of MIF in PsA and its potential as a biomarker or therapeutic target.

MS. Like PsA and SLE, MS is another autoimmune disorder in which MIF plays a crucial role. MS is the most common non-traumatic disabling disease affecting young adults (147). While its underlying cause remains uncertain, it is described as a chronic, immune-mediated demyelinating disease of the central nervous system (CNS) (89). MS is commonly viewed as a two-stage phenomenon, with early inflammatory processes driving the relapsing-remitting form and later neurodegeneration contributing to a non-relapsing progressive phase (147). During neuroinflammation, macrophages and microglia are considered significant sources of MIF in the CNS. Increased MIF levels have been found in patients with progressive MS, which are correlated with disease severity and progression (147).

A 2019 study by Cavalli *et al* (148) suggested that upregulation of the MIF cytokine family signature may occur in $CD4^+$ T cells in patients with clinically isolated syndrome, potentially contributing to MS pathogenesis and serving as an effective biomarker and therapeutic target. The expression of MIF, CXCR4 and CD74 appears to be tightly regulated via negative feedback mechanisms (149). Similarly, Guan *et al* (150) demonstrated using a murine model of experimental autoimmune encephalomyelitis (a model of human MS) that inhibiting the MIF-CD74 interaction suppresses microglial M1 polarization and induces an anti-inflammatory response. B cell arrest in early maturation stages (implicated in MS onset) has been partially associated with MIF downregulation, which correlates with decreased CD74 and increased CXCR4 expression (89,149,151,152). Upregulation of CXCR4 suppresses Fas, reducing the clearance of autoreactive immune cells and allowing naive B cells to escape immune tolerance (89,149,152).

The relationship between the MIF-173G>C polymorphism and MS remains under investigation. Current evidence suggest no association with disease susceptibility in the Turkish population (129). However, in the Mexican Mestizo male population, this polymorphism may act as a male-specific modifier, influencing disease severity and progression (153).

Novel therapeutic strategies targeting MIF continue to emerge for MS. For instance, Dra1 constructs strongly inhibit the activation and recruitment of brain-infiltrating T cells and $CD11^+CD45^{high}$ myeloid cells, which express elevated levels of CD74 following CNS damage. These constructs antagonize CD74 with high affinity, resulting in diminished MIF signaling. This treatment approach also shows potential in methamphetamine addiction and traumatic brain injury (154). Additionally, iguratimod (IGU), an anti-rheumatic drug, exhibits selective MIF inhibition both *in vitro* and *in vivo*, and demonstrates additive effects with glucocorticoids in autoimmune encephalitis models (155). Another promising drug is ibudilast, a MIF and phosphodiesterase inhibitor, which has shown efficacy in slowing brain atrophy in progressive MS (156). It is worth noting that MIF levels are not useful for distinguishing responders from non-responders to glucocorticoid treatment in patients with acute optic neuritis, as they reflect only ongoing inflammation seen in long-term MS progression (157).

AA. As a more organ-specific autoimmune condition, AA exemplifies how the immunomodulatory role of MIF impacts localized immune privilege. AA is characterized by non-scaring hair loss, ranging from bald patches to total scalp involvement. The disease emerges when immune privilege is lost in hair follicles, and MIF has been implicated in this process due to its ability to suppress natural killer cell activity (92,158,159). Genetics, emotional stress and autoimmunity all play an important role in the pathogenesis of AA (158).

Based on these findings, Eldesouky *et al* (158), investigated the involvement of MIF in AA and vitiligo using a small cohort comprising 22 patients with AA, 20 patients with vitiligo and 20 healthy controls. The results showed that MIF levels were significantly elevated in both AA (8.477±4.1761 ng/ml) and vitiligo vulgaris (3.930±2.7071 ng/ml) compared with controls (0.725±0.5108 ng/ml) ($P<0.01$). Furthermore, MIF concentrations were positively correlated with disease severity in both conditions. The authors concluded that MIF may play a significant role in the pathogenesis of AA and vitiligo, and that targeting MIF could represent a promising therapeutic approach.

In 2020, Oh *et al* (160) investigated the application of conditioned medium (CM) from human umbilical cord blood-derived mesenchymal stem cells (MSCs) to improve hair growth and developed a method to reliably produce this optimized CM. Their results demonstrated that MIF was essential for the effects of the primed MSC-derived CM and identified it as a key modulator of the hair growth-related protein VEGF in dermal papilla cells. These findings strongly suggest that this method could counteract hair loss and serve as a promising agent for hair restoration.

Vitiligo. Just as AA involves the immune targeting of hair follicles, vitiligo is another organ-specific autoimmune disease, marked by depigmentation due to $CD8^+$ T cell-mediated melanocyte destruction. The average lesion is a totally amelanotic, non-textured and white macule, with progressive disfigurement (161-163). Emerging evidence suggests that vitiligo is associated with a weakened antioxidant system,

leading to free radical-mediated melanocyte death or deregulated melanogenesis that may trigger autoimmunity (164). MIF concentrations vary throughout the disease stages, potentially acting as an inflammatory setpoint by regulating the release of proinflammatory molecules (161,162,164).

A Chinese study found that the MIF-173G/C polymorphism and increased serum MIF levels were associated with active non-segmental vitiligo (NSV), which accounts for 90% of vitiligo cases (165). In western Mexico, the-794 CATT 5-8 and -173 G>C MIF polymorphisms are similarly associated with increased NSV risk. Moreover, both serum and *in situ* MIF levels are correlated with active disease status (161). Research has proposed that MIF may play a fundamental role in skin development (161). Both soluble CD27 (sCD27) and MIF are considered reliable serum biomarkers for disease progression, although sCD27 may offer greater predictive value (162,166).

Vitiligo is currently treated with topical corticosteroids, immunomodulatory agents, vitamin D analogs, antioxidants, phototherapy, laser therapy and surgery. Narrowband UVB (311-313 nm) remains the standard treatment (162,163). Novel therapies targeting MIF-related pathways include JAK inhibitors, *N*-acetyl-p-benzoquinone imine, isoxazoline imine conjugates and amino acid-benzaldehyde analog conjugates (162,163). JAK inhibitors are currently in phase II trials for topical use in patients with vitiligo (163).

RA. RA is a chronic, invasive autoimmune disease characterized by synovial inflammation, joint erosion and bone resorption. Although its etiology is not fully understood, macrophages are one of the most abundant cell types in the synovium. Their excessive activation, enhanced anti-apoptotic capacity and increased production of proinflammatory cytokines contribute to RA pathogenesis (167-170). MIF plays a central role in sustaining inflammation in RA by promoting the production of proinflammatory cytokines and tissue-degrading enzymes. MIF stimulates MIF synovial fibroblast proliferation, neutrophil chemotaxis and osteoclast differentiation (168). Notably, a Swedish study reported decreasing MIF levels in patients with RA, contrary to the commonly considered association between MIF and RA severity (171). A 2017 meta-analysis including Asian, Latin American and Caucasian populations showed significantly elevated circulating MIF levels in patients with RA and found associations between MIF-173C/G and -794CATT5-8 polymorphisms and disease susceptibility (167). In southern Mexico, these MIF polymorphisms were related to disease activity but not susceptibility, contrasting with findings from Western Mexico (172). Further research is needed to clarify these population-specific discrepancies, particularly in the cell-type-specific transcriptional regulation of MIF variants.

Additionally, MIF-173C/G and-794CATT5-8 polymorphisms also appear to influence Th17-associated cytokine secretion in peripheral blood mononuclear cells from patients with Cushing's syndrome and RA. Their differential expression suggests a regulatory role of MIF promoter haplotypes in inflammatory profiles (173). More recently, MIF has been implicated in the regulation of Th2 cytokines such as IL-25, IL-31 and IL-33, which may have immunomodulatory roles in RA (174).

The discovery of CD74 autoantibodies in the serum of patients with RA supports the role of CD74 as a T-cell antigen in spondyloarthritis, eliciting Th1 and Th17 responses (175). A study examining MIF receptor expression at different stages of RA emphasized the need for further investigation into sCD74 as a MIF decoy receptor, capable of down regulating receptor signaling. The same study identified CXCR7 as a scavenger receptor that stabilizes CXCR4 under inflammatory conditions by preventing its internalization and degradation (176). Since 2018, new treatment options have emerged, including Z-590, a MIF inhibitor, and isopsoralen (IPRN), both showing promise in controlling RA-associated inflammation (168,170).

8. Advances in the therapeutic strategies targeting MIF

The MIF/D-DT/CD74 axis has emerged as a promising therapeutic target not only in oncology [as extensively reviewed by Valdez *et al* (177)] but also in autoimmune, inflammatory and fibrotic diseases. Valdez *et al* (177) provide a comprehensive overview of current research and clinical trials targeting this axis in cancer, emphasizing both its therapeutic potential and the challenges associated with this approach. Their report discusses multiple therapeutic agents, including imalumab, ibudilast and milatuzumab, each demonstrating varying degrees of clinical success. However, key challenges remain, including limited efficacy and the unclear contributions of MIF and oxidized MIF in tumorigenesis (177).

Therapeutic strategies targeting MIF and its homolog D-DT are gaining traction as innovative approaches to overcoming tumor immune evasion and resistance to immune checkpoint inhibitors (ICIs) (178-180). Both cytokines are implicated in several cancer hallmarks, such as proliferation, immune suppression, angiogenesis and metastasis. Inhibition of MIF using small molecules such as 4-IPP has demonstrated potent anti-tumor effects in melanoma models, including tumor burden reduction, downregulation of programmed death ligand-1 and HIF1α as well as metabolic reprogramming. These changes are accompanied by increased CD8□ T cell infiltration and a shift in macrophage polarization toward a proinflammatory M1 phenotype (178,179). Similarly, D-DT inhibition reduces proliferation markers and increases apoptotic markers in melanoma cells, although its role is less well characterized (180).

Notably, combination therapies targeting both MIF and D-DT have produced synergistic effects. Dual blockade has been linked to decreased infiltration of MDSCs, increased recruitment of $CX3CR1^{+}$ patrolling monocytes and depletion of immunosuppressive TAMs, collectively fostering a more immunogenic TME (181). These benefits are further enhanced when dual cytokine inhibition is combined with programmed death-1 or CTLA-4 checkpoint inhibitors, leading to improved tumor control, prolonged survival and durable antitumor memory in murine models of melanoma and CRC (178,181). Supporting these findings, transcriptomic data from patients with melanoma revealed that lower MIF and D-DT expression (or higher CD74:MIF and CD74:D-DT ratios) are correlated with improved overall survival and increased immune cell infiltration, suggesting both prognostic and predictive value (177). An overview of these therapies is provided in Table VI. Collectively, these insights underscore the MIF/D-DT axis as a critical immunoregulatory hub and

Table VI. Cancer-related MIF therapeutic approaches.

Therapy	Mechanism/target	Application	Effect	(Refs.)
Imalumab, ibudilast and milatuzumab 4-IPP	Targets the MIF/DDT/CD74 axis	Oncology (clinical trials)	Variable efficacy; under ongoing evaluation.	(177)
	MIF inhibition	Melanoma models	Reduced tumor burden, PD-L1 and HIF1α downregulation, metabolic reprogramming and M1 macrophage polarization.	(178,179)
D-DT inhibition	D-DT inhibition	Melanoma cells	Reduced proliferation and increased apoptosis.	(180)
MIF + D-DT dual blockade	Simultaneous MIF and D-DT inhibition	Melanoma and colorectal cancer (murine models)	Decreased MDSCs, increased $CX3CR1^{+}$ monocytes, TAM depletion and improved tumor control and survival.	(178,181,190)
Checkpoint inhibitors + MIF/D-DT blockade	Combination with PD-1/CTLA-4 inhibitors	Melanoma and colorectal cancer (murine models)	Enhanced antitumor response, prolonged survival and durable memory	(178,190)
MN123 + RSL3	MIF tautomerase inhibition + ferroptosis inducer	HR and ferroptosis studies	Enhanced ferroptosis sensitivity.	(188)
1-carbomethoxy-5-formyl-4,6,8-Trihydroxyphenazine	Inhibition of ICBP90-regulated MIF expression	Macrophages with high MIF genotypes	Selective reduction of MIF expression.	(189)

PD-L1, programmed death-ligand 1; HIF1α, hypoxia-inducible factor 1-α; MDSCs, myeloid-derived suppressor cells; TAM, tumor-associated macrophage; PD-1, programmed death-1; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICBP90, inverted CCAAT box binding protein of 90 kDa.

viable target for enhancing ICI efficacy and overcoming resistance.

Beyond oncology, a growing body of research explores MIF-targeting strategies in other disease contexts. One such agent is IGU, or T-614, which selectively inhibits MIF tautomerase activity. This inhibition reduces B cell proliferation, cytokine release and TNF-α-mediated inflammation. IGU also modulates immune homeostasis by regulating Th17 and Treg cells, enhancing glucocorticoid efficacy, and serving as a steroid-sparing agent. These properties support its application in diseases such as RA, lupus and MS, fibrotic conditions and acute disorders such as acetaminophen-induced injury (182-184). ART, primarily known for its antimalarial properties, also modulates MIF activity. ART reduces parasitemia and improves hemoglobin levels by counteracting MIF, making it a potential therapy for anemia associated with parasitic infections. Additionally, ART exerts immunosuppressive effects by inhibiting MIF signaling and reducing proinflammatory mediators, highlighting its promise in treating inflammatory and autoimmune disorders (185,186). IPRN, a compound derived from *Psoralea corylifolia*, has shown therapeutic potential in RA by targeting MIF. IPRN inhibits cytokine production, cellular migration and proangiogenic activity in RA fibroblast-like synoviocytes. *In vivo* studies using collagen-induced arthritis models demonstrate that IPRN reduces paw thickness, arthritis scores and circulating inflammatory cytokines, reinforcing its candidacy as a novel RA therapy (168).

Advancements in small-molecule inhibitors have further broadened the therapeutic landscape of MIF inhibition. Guo *et al* (187) identified benzopyran and triazole derivatives as selective MIF inhibitors. Benzopyran compounds block MIF-CD74 binding and reduce ERK phosphorylation, while triazoles exhibit dose-dependent inhibition of MIF-induced proliferation. Chen *et al* (188) explored the connection between MIF, homologous recombination and ferroptosis, identifying MN123 as a non-competitive tautomerase inhibitor that sensitizes cells to ferroptosis when combined with RSL3. In parallel, Li *et al* (189) investigated ICBP90, a transcriptional activator of MIF, and its interaction with a MIF promoter microsatellite. Their study showed that the small molecule, 1-carbomethoxy-5-formyl-4,6,8-trihydroxyphenazine (CMFT), preferentially downregulates MIF in macrophages with high-expression genotypes.

Table VII. Autoimmunity-related MIF therapeutic approaches.

Therapy	Mechanism/target	Application	Effect	(Refs.)
Iguratimod (T-614)	MIF tautomerase inhibition	RA, lupus, MS, fibrotic diseases and acetaminophen-induced injury	Reduced B cell proliferation, cytokine release, Th17/Treg modulation and glucocorticoid enhancement.	(182-184)
Artesunate	MIF modulation	Anemia in parasitic infections and inflammatory and autoimmune diseases	Reduced parasitemia, MIF inhibition and decreased inflammatory mediators.	(185,186)
Isopsoralen	MIF inhibition	RA (*in vitro* and CIA models)	Reduced cytokine production, FLS migration, arthritis score and serum inflammation markers.	(168)
Benzopyran and triazole derivatives	MIF inhibition (binding and ERK pathway)	Experimental models	Inhibited MIF-CD74 binding, ERK phosphorylation and MIF-induced cell proliferation.	(187)

RA, rheumatoid arthritis; MS, multiple sclerosis; Th17, T-helper 17; Treg, regulatory T cells; FLS, fibroblast-like synoviocytes; ERK, extracellular signal-regulated kinase; CIA, collagen-induced arthritis.

Taken together, these studies, complemented by the findings of Valdez *et al* (180), highlight the broad therapeutic promise of MIF inhibition. While challenges remain in targeting the MIF/D-DT/CD74 axis in oncology, the expanding body of evidence across various pathologies suggests that fine-tuned modulation of MIF activity and expression could yield significant clinical benefits. A summary of MIF-targeted therapies in autoimmune and inflammatory conditions is provided in Table VII. Future research should prioritize dosing optimization, long-term safety and the development of rational combination therapies to fully harness the potential of MIF-targeted interventions across cancer, autoimmunity and inflammatory diseases.

Nevertheless, according to current literature and a review of publicly available reports from both the U.S. Food and Drug Administration and the European Medicines Agency, to the best of our knowledge, there are no approved therapeutic options that specifically target MIF currently in clinical use. However, research and development efforts are ongoing. Notably, a 2023 U.S. patent (no. US11584717B2), assigned to Yale University, describes MIF modulators that are presently undergoing *in vitro* and *in vivo* testing. Among these, CMFT has been the subject of early-stage evaluation, as reported by Li *et al* (189). In addition, several existing compounds, such as IGU, ART and IPRN, have demonstrated MIF-modulating or inhibitory effects in the context of autoimmune diseases. Despite this, these agents are not specific MIF inhibitors and instead exert broader immunomodulatory actions, limiting their precision in targeting MIF-driven pathways

9. Conclusions

MIF has emerged as a uniquely multifunctional cytokine at the crossroads of immunity, inflammation and tissue homeostasis. Unlike other proinflammatory mediators, MIF influences both innate and adaptive immune responses through its diverse receptor interactions (including CD74, CD44, CXCR2, CXCR4 and CXCR7) and enzymatic activity, allowing it to regulate immune cell recruitment, survival and function across a wide range of physiological and pathological contexts. The dual role of MIF as both a protector in homeostatic repair and a driver of chronic inflammation and tumorigenesis sets it apart as a compelling and complex target for therapeutic intervention.

Notably, polymorphisms in the MIF gene (such as-794 CATT5-8 and -173G>C) not only increase susceptibility to autoimmune and oncological diseases but also modulate disease severity and treatment responsiveness, suggesting the potential of MIF as a personalized biomarker. Therapeutic strategies that inhibit MIF activity, such as small-molecule inhibitors (including ISO-1 and 4-IPP), immunomodulatory agents (including IGU) and proteolysis-targeting chimeras, have demonstrated efficacy in preclinical models of cancer, autoimmune disease and neuroinflammation. Despite this progress, key questions remain. The precise regulation of MIF expression, the long-term systemic effects of its inhibition and the dynamics of its interaction with various receptors in distinct tissue microenvironments are areas ripe for exploration. Additionally, the development of receptor-specific inhibitors may unlock new therapeutic windows with reduced side effects.

MIF research is uniquely positioned to reshape current paradigms in immunotherapy and inflammation-driven pathology. As our understanding of its molecular mechanisms deepens, MIF stands not only as a marker of disease but also as a gateway to precision medicine strategies that can modulate immune responses with unprecedented specificity. The continued integration of genetic, biochemical and clinical insights will be essential in translating MIF-targeted therapies into viable, mass-scale solutions across oncology, autoimmunity and regenerative medicine.

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Authors' contributions

GCM and GAN reviewed the literature and wrote the manuscript. RRP, JFMV and UDM reviewed and critically revised the manuscript. LABH defined and supervised the contents of the text and figures generated and conceived the original idea for this review. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (ChatGPT, https://chatgpt.com) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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