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Review

Macrophage Migration Inhibitory Factor: Its Multifaceted Role in Inflammation and Immune Regulation Across Organ Systems

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Key Words
Macrophage Migration Inhibitory Factor (MIF) • Immune regulation • Inflammation • Biomarker • Therapeutic targeting

Abstract
Macrophage Migration Inhibitory Factor (MIF) is a pleiotropic cytokine that acts as a central regulator of inflammation and immune responses across diverse organ systems. Functioning upstream in immune activation cascades, MIF influences macrophage polarization, T and B cell differentiation, and cytokine expression through CD74, CXCR2/4/7, and downstream signaling via NF-κB, ERK1/2, and PI3K/AKT pathways. This review provides a comprehensive analysis of MIF's mechanistic functions under both physiological and pathological conditions, highlighting its dual role as a protective mediator during acute stress and as a pro-inflammatory amplifier in chronic disease. MIF's involvement in autoimmune disorders, neurodegeneration, metabolic syndromes, infectious diseases, and oncogenesis is examined, with particular attention to its contribution to immune dysregulation, immune escape, and the shaping of inflammatory microenvironments. Its clinical relevance as a biomarker is underscored by associations between elevated serum levels, polymorphic variants such as the -173 G>C SNP, and disease susceptibility, progression, and therapeutic response. Advances in therapeutic strategies are also discussed, including the development of small-molecule inhibitors, MIF-2-specific antagonists, CD74-targeted therapies, and gene-based interventions. Taken together, emerging evidence positions MIF as both a diagnostic indicator and a therapeutic target, with its broad regulatory functions across immune, vascular, and metabolic pathways emphasizing

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its relevance in precision immunotherapy and its potential to serve as a strategic axis in the future of translational medicine.

Introduction

Macrophage Migration Inhibitory Factor (MIF) was found in the 1960s, a time that changed immunologists' thoughts [1]. At its earliest, MIF was defined as something that came from activated lymphocytes, stopped macrophages from moving, and helped control inflammation [2]. MIF was one of the first lymphokines ever found, even before the cytokine classification system was developed [3, 4]. In the past five decades, MIF has moved from being a basic migration blocker to an important, single- functional, and persistent cytokine involved in the immune system, tissue injury responses, and chronic diseases [5, 6]. Unlike inducible cytokines, MIF is preformed and stored within cells, so it can be released quickly when the cells detect hypoxia, infection or glucocorticoids. MIF acts as a first responder cytokine that comes before and strengthens other inflammatory events. MIF is also unique in that it can reduce the effects of glucocorticoids, which normally reduce inflammation, and thus helps inflammation to continue under stressful conditions [7, 8]. MIF persists in promoting inflammation and also resists the action of glucocorticoids; it is involved in many diseases for a long time. MIF binds to CD74 and co-receptors CXCR2, CXCR4, and CXCR7 at the molecular level, which helps to control it signaling. As a result of these pathways, MIF turns on signaling cascades such as MAPK/ERK1/2, PI3K-Akt, and NF-κB, which increase the release of proinflammatory cytokines (such as IL-6 and TNF-α), help cells survive, promote blood vessel formation, and prevent cell death [9, 10, 11]. As a result, MIF is positioned between immunity, inflammation, and cellular remodeling. Its ability to activate the NLRP3 inflammasome means MIF is important for sterile inflammation, infectious diseases, and systemic cytokine responses. MIF is known to be overproduced in many different clinical conditions. In rheumatoid arthritis and systemic lupus erythematosus, MIF helps create Th1/Th17 cells, increases the survival of macrophages, and contributes to damage in the body [12]. In these disorders, it weakens the blood- brain barrier and encourages microglial cells to become active, leading to inflammation in the brain and a decrease in cognitive function [13]. MIF plays a role in increasing inflammatory cardiomyopathy and atherosclerosis by affecting the function of the endothelium and recruiting monocytes [14]. MIF gene polymorphisms, especially the - 173G/C SNP, have been connected to higher disease risk, lower response to glucocorticoids, and different reactions to treatments [7].

More attention is being given to MIF helps tumors escape immune detection, form new blood vessels, and adapt their metabolism in the TME. Different MIF receptors present on TAMs and MDSCs allow MIF to shape the immune environment in a way that supports tumor growth and makes tumors resistant to checkpoint inhibitors [15, 16, 17]. In studies of ovarian, colorectal, and glioblastoma, MIF has been found to play a role in chemoresistance and the reorganization of stromal cells, usually acting as a negative prognostic marker [18]. It is also known to support the protection of tissues in situations of acute stress. Studies have concluded that the MIF/CD74 system can reduce kidney damage after ischemia and help heal kidney epithelial cells [19, 20]. Since MIF may be protective or harmful in different situations, every therapy for MIF should be custom-made for each tissue. The numerous functions of MIF imply that it is currently considered a biomarker, an object of therapy, and a novel perspective in grasping inflammatory and immune conditions. Nevertheless, some aspects of how receptors and ligands interact and how they influence one another are still not exactly comprehended by researchers and how tissues differ in signaling as well as how TNF may have various beneficial or harmful properties. To explain how basic immunology is utilized, this review attempts to describe how or why MIF was discovered, its molecular characteristics, the mechanisms it employs, effects of its action on a variety of organs as well as how the discovery of MIF is studied clinically and medically treated.

Review Objectives

1. The review will be arranged in light of the following objectives in order to address a full picture of the recent development of Macrophage Migration Inhibitory Factor (MIF) within immunology and diseases:
2. To give a comprehensive study of the molecular framework, signaling pathways and regulatory processes of MIF in inflammation and immune regulation
3. To review the organized assessment of organ-specific functioning of MIF and its role in pathogenesis of autoimmune, infectious, metabolic, neurodegenerative, and malignant diseases to assess MIF's potential as a diagnostic biomarker and therapeutic target, while identifying gaps in current knowledge and translational challenges

Historical Evolution and Cross-Species Conservation of MIF

From Discovery to Molecular Reclassification

Macrophage Migration Inhibitory Factor (MIF) was initially discovered in the 1960s as being among the first soluble mediators with the capability to regulate immune cell activity. Originally classified as a lymphokine due to its property to restrain macrophage movement, MIF's utility scope was merely appreciated in part before the establishment of the cytokine paradigm. Later studies, especially after it was rediscovered in the 1990s, restyled MIF as a multifunctional cytokine capable of resisting glucocorticoid-induced suppression, sustaining pro-inflammatory signaling, and coordinating the recruitment of immune cells [5]. MIF is now defined not only by its cytokine role but also by its chemokine-like behavior, interacting with classical cytokine receptor CD74 and non-cognate chemokine receptors including CXCR2, CXCR4, and CXCR7. Although the functional interaction of MIF with its main receptor CD74 and chemokine co-receptors such as CXCR2, CXCR4, and CXCR7 is supported by a wide range of experimental evidence, the precise structural description of these interactions is still poor. Currently, no crystallographic or cryo-EM studies have provided the exact molecular conformation of MIF complexed to these receptors. This limitation inhibits a thorough appreciation of how MIF acts on its targets at the atomic scale. Key factors, receptor binding geometry, possible structural changes on ligand binding, and the co-receptor cooperation dynamics are unknown. Most is learned through indirect evidence, such as mutational analysis, molecular modelling, and biochemical assays, which offer only partial insight into mechanisms of MIF receptor specificity and activation of downstream signaling. These receptor interactions trigger MAPK/ERK, PI3K-Akt, and Src kinase signaling cascades, situating MIF at the intersection of immune activation and inflammatory homeostasis [9, 21]. Unlike traditional cytokines, MIF is preformed, stored intracellularly, and rapidly released upon cellular stress, giving it the unique biological function of an immediate-response amplifier in both innate and adaptive immunity.

Evolutionary Conservation and Structural Integrity

At the molecular level, MIF is among the most phylogenetically conserved cytokines. Comparative genomics reveals that MIF orthologs exist across protists, plants, invertebrates, and vertebrates, reflecting a highly conserved primary structure, particularly in the tautomerase active site, the N-terminal proline (Pro1), and Lys32, which are essential for redox signaling [22]. Although Pro1 and Lys32 are conserved residues, their key functional significance goes beyond redox signaling. Pro1 is the catalytic nucleophile for the tautomerase active site, and its position in the structure is important for enzymatic function. The biological relevance of MIF tautomerase activity is not known but studies by Pantouris and his colleagues [23] suggested that point mutations of Pro1 or other proximal residues strongly impair MIF cytokine activity, therefore enzymatic integrity is needed to perform its immunomodulatory functions. The disulfide bonded Cys 56-Ala-Cys59 motif that is outside the scope of the current discussion, is also critical to redox sensitivity. This motif undergoes a conformational

change in reaction to oxidative or other pressures as well, altering the structural packaging of MIF and its ability to bind its receptors. These sites as a combination also enhance catalytic activity in this combined form hence responding further to the role of MIF under pathological conditions. Functional parts, such as enzyme-binding areas and receiver binding sites, are preserved levels over 85 portions in the eukaryotic taxa, despite a specified divergence in the loop regions or surface-open residues. Such conservation implies powerful evolutionary constraint so that the combinatorial biology of both MIF present inside cells as an intra-redox therapeutic protein and outside cells as a pro-inflammatory mediator are vital to host defense and cellular homeostasis. Stereospecific tautomerase activity in simpler organisms is found in MIF, and is probably the driving force behind cellular redox equilibrations. In mammals tautomerase activity is reduced, but it serves a functional purpose in the presence of oxidative stress.

The expediency of research on MIF redox chemistry has been followed by recent studies that have contributed to the know-how with the highlighting of the distinct biochemical peculiarities of the oxidized form of MIF. The tertiary structure of oxidized MIF (oxMIF) is altered and its receptor binding is also altered relative to reduced MIF. Schinagl and his team [24] demonstrated that oxMIF assumes a comparative configuration that is neither totally catalytically true-blue nor does it rebuild extraordinary pro-inflammatory properties. Sajko with colleagues [25] further established that MIF also suffers redox alterations that influence its affinity to its receptors, which influence CD74-mediated signaling in conditions of oxidative tissue environments. Furthermore, Thiele and colleagues [26] have already identified redox dependent residues in MIF that alter their structure and determine stability and cytokine-like activity of MIF in pathological conditions of stress. These findings point at the fact that the redox modulation is maintained as a regulatory mechanism, and MIF is able to modify its activities as a reaction to tissue redox state. These biochemical features underscore MIF as a primordial immunotransducer, to sense metabolic stress and couple its response to the watchdog immune system, well before the origin of the professional immune system cells.

Functional Validation in Cross-Kingdom Models

Non-mammalian model systems support the universality of MIF function. In a basal chordate Ciona robusta, whose immune system is highly primitive, MIF, stimulated with lipopolysaccharide (LPS), activates Toll-like receptor (TLR) signaling cascades and, consequently, NF-x B activity and secretion of cytokines [27]. This observation highlights that MIF immunoregulatory activities have co-evolved with the most ancient elements of the innate immune recognition [28]. The removal of the MIF homolog of live-attenuated parasites of Leishmania major showed a marked increase in CD4+ T cell mediated protective immunity, identifying the factors of pathogen-derived MIF homologs that could therefore be considered as immune-suppressive molecules with the ability to sub-optimize the host response. On the same note, during African trypanosome infection, MIF interplays with IL-10 in a Yin-Yang relationship binding host immunity and parasitism survival by the action on dendritic cells and suppression of T-cells [29]. Such studies not only affirm the ancient immunomodulatory utility of MIF but also reveal that immune evasion mechanisms in parasites and tumors may co-opt MIF signaling, a critical insight for translational immunotherapy.

Evolutionary Function in Modern Pathologies

The basic functions of MIF are still associated with disease in today's world. In RA and SLE, MIF helps synovial fibroblasts live longer, supports the growth of Th17 cells, and resists the effects of glucocorticoids, making inflammation and damage worse [30]. In atherosclerosis and myocardial infarction, MIF promotes the recruitment of inflammatory macrophages, endothelial dysfunction, and fibroblast activation, thereby shaping both acute and chronic cardiovascular responses [31, 32]. Functionally, MIF's ability to operate via CD74-Src-PI3K-Myosin II signaling supports dendritic cell migration, critical for immune surveillance and antigen presentation [21]. This ancient migratory role, retained from invertebrate immunity,

reemerges in tumor-associated macrophage dynamics, where MIF orchestrates myeloid-derived suppressor cell (MDSC) recruitment and tumor immune evasion [33, 34].

Neuroimmune Interface and Behavioral Evolution

Evolutionary psychoneuroimmunology is a new field, and here, MIF's lasting presence in the CNS could link inflammation to behavior. Yirmiya [35] proposes that MIF contributes to understanding why depression is inflammatory and might influence mood, thinking and responses to stress. As a result, MIF now plays a part in evolutionary behavior and in immunity.

Molecular Structure, Composition, and Genetic Regulation of MIF

Structural Architecture and Functional Interfaces

Macrophage Migration Inhibitory Factor (MIF) is a well-kept protein weighing 12.5 kDa, is formed by three identical subunits, and each subunit is involved in forming the main channel that determines its structure and function [36]. Hydrophobic and hydrogen bonds give this shape stability, allowing the structure to perform as an enzyme and receptor. Pro1 is the main role of MIF, which works to turn one chemical into another, but this is not important in humans, according to Chen and colleagues [37]. On top of being a tautomerase, MIF also acts as an oxidoreductase whenever cells deal with oxidative stress, so it could have once played a role in managing oxygen levels for early life. Alpha Fold multimer modelling supports the idea that MIF forms strong complexes with CD74 and JAK2, which activate the MAPK and PI3K-Akt pathways [38]. In addition, the Arg-Leu-Arg (RLR) area at the MIF-CXCR4 site lets MIF communicate with the chemokine receptor, proving it has a chemokine function and can regulate the white blood cells that are recruited and move.

MIF's receptor-mediated signaling and its binding to CD74 and related chemokine receptors trigger downstream intracellular processes in immune and inflammatory control, as shown in Fig. 1. Schematic illustration of MIF initiated signaling pathways: The diagram demonstrates that Macrophage Migration Inhibitory Factor (MIF) can interact with the cell surface receptor CD74 and with co-receptors, (CXCR2, CXCR4, and CXCR7). These events cause an intracellular cascade of signaling events which include MAPK/ERK signaling

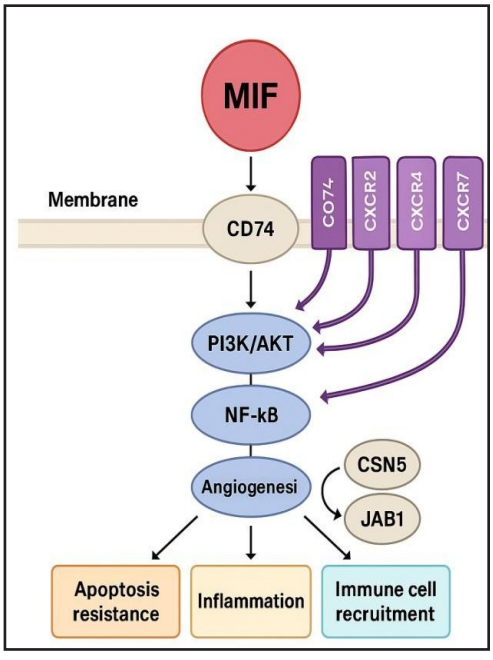

Fig. 1. MIF Signalling Pathways and Functional Outcomes. MIF's receptor-mediated signalling and its binding to CD74 and related chemokine receptors trigger downstream intracellular processes in immune and inflammatory control, as shown in Figure 1. Schematic illustration of MIF initiated signalling pathways: The diagram demonstrates that Macrophage Migration Inhibitory Factor (MIF) can interact with the cell surface receptor CD74 and with co-receptors, (CXCR2, CXCR4, and CXCR7). These events cause an intracellular cascade of signalling events which include MAPK/ERK signalling pathways, PI3K/AKT pathways and NF- KB signalling pathways. These molecular networks have the effect of controlling different cell functions including generation of cytokines, surviving signals, angiogenesis and blocking apoptotic pathways. Besides, MIF has nuclear regulatory actions with the intracellular proteins CSN5 and JAB1. Collectively, it is possible to note the integrative role of MIF in linking extracellular signals toward both inflammatory and metabolic regulation of gene expression as outlined by this figure.

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Interactions with CD74, CXCRs, and Downstream Regulation of Proliferation, Apoptosis, and Angiogenesis [39].Signals of MIF commence when it becomes stimulated. Upon binding with CD74 and CD44 and CXCR 2/4/7 MIF leads to activation of SRC-kinase and transmission of mapping through MAPK/ERK and PI3K /AKT pathways. They manage transcription factors, encourage cell growth, and stop cells from dying by reducing p53 and turning on Bcl-2 and Bcl-xL, as shown in Fig. 2. By regulating HIF-1α, MIF causes cells to make angiogenic factors, including VEGF and IL-8. MIF also works within the cell by interacting with CSN5 and JAB1 to bring about more effects in the nucleus. MIF signals help reveal its role in inflammation, escaping recognition by the immune system, promoting cancer, and influencing tissue alterations.

Regulatory Polymorphisms and Transcriptional Control

The gene for MIF in humans is located on chromosome 22q11.2 and is managed by stress and inflammation-sensitive elements such as AP-1, NF-κB, and CREB [6]. Recent studies found that the presence of transcription factors at enhancers can switch on or off gene expression, with only minor changes in enhancer accessibility causing a big increase in MIF expression [40]. Especially, the -173G/C SNP (rs755622) in the MIF promoter region is associated with higher MIF levels and a greater risk of disease. Meta- analyses have found that the C allele raises the risk of inflammatory diseases by 1.6-2.4 times and leads to poorer outcomes in hepatocellular carcinoma and rheumatoid arthritis [41, 42]. There are other variants, including rs3063368, that have been linked to worse results in acute kidney injury and pemphigus vulgaris [43, 44]. Taken together, these polymorphisms suggest that host genetics can influence MIF-related diseases and their responses to treatment.

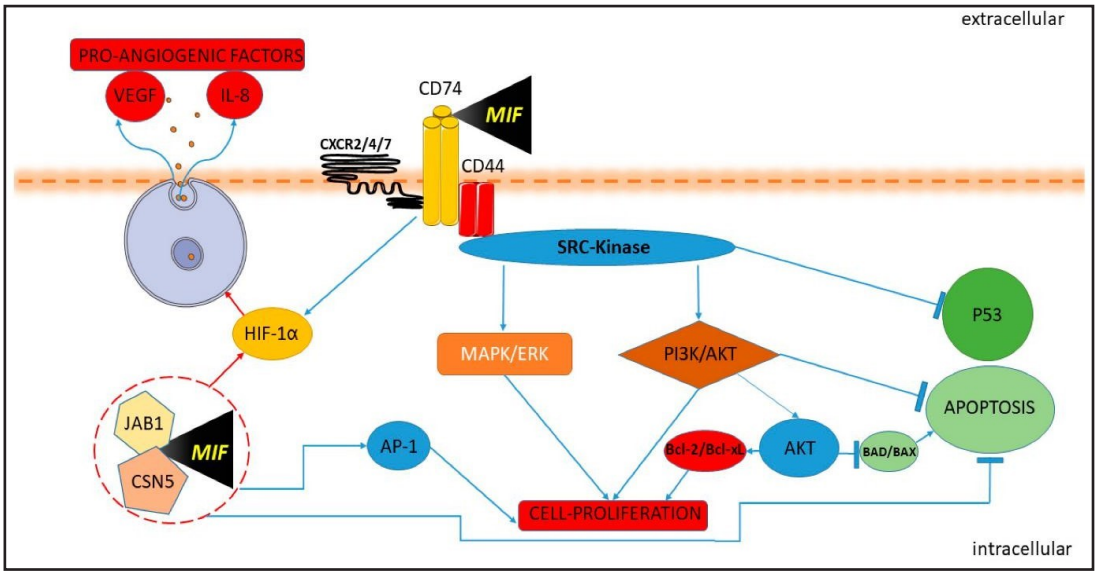

Fig. 2. MIF-Mediated Signalling Cascade: Interactions with CD74, CXCRs, and Downstream Regulation of Proliferation, Apoptosis, and Angiogenesis (Cavalli et al., 2020).

Epigenetic and Non-Coding RNA Modulation

Apart from genetics, MIF expression can be controlled by epigenetic means, including changes to chromatin and histones, and non-coding RNAs. Tumors that have metabolic problems show lipid-related changes in histones that support high MIF levels and lead to immune cell dysfunction, mainly in the natural killer (NK) cell exhaustion setting [45]. In gastric cancer, chromatin accessibility profiling confirmed that MIF is found in regions of open chromatin that are rich in immune cells, which may explain why MIF is linked to tumor aggressiveness [46]. MIF-AS1 and other regulatory lncRNAs have been found to induce EMT in breast cancer by removing miR-1249-3p from the system, which then dysregulates MIF's downstream targets [47]. Furthermore, blocking enhancer- bound long non-coding RNAs or transcription factor groups using CRISPR/Cas9 has been successful in controlling MIF expression, which may help with future epigenome-based treatments [48, 49].

Pharmacological Inhibition and Allosteric Targeting

Pharmacological inhibition of MIF has advanced considerably through the development of allosteric modulators that interfere with MIF function without disrupting its trimeric structure. Early compounds like ISO-1 target the Pro1-dependent tautomerase pocket, while newer agents like Iguratimod, picolinoyl peptidomimetics, and solvent channel blockers modulate MIF activity via structurally preserved but catalytically independent regions [50, 51]. These agents were shown to have effectiveness in an array of preclinical conditions. In liver injury and acetaminophen, Iguratimod has been shown to reduce mortality by simultaneously reducing oxidative stress and managing inflammation, and selective MIF inhibition in acute myeloid leukemia ends the leukemia process by arresting the cell cycle [52]. There is also a structural similar homolog of MIF known as MIF-2 (D-DT) which also is a potential drug target and selective inhibitors have shown positive outcomes regarding inflammatory and autoimmune diseases [53]. The two are similar in that both MIF and MIF-2 employ identical receptors, but these two share different functions, and this helps them distinguish between them in effective drug design.

Mechanisms of Action and Signaling Pathways of MIF

MIF is the most important component of connectivity of inflammation, stress and immune signaling that user to restrain the action of a cell. MIF produces distinct tasks with the help of binding the receptors of the cell surface and catalyzing inside processes like sustaining life, enhancing immune system, causing chronic inflammation and reducing responsiveness to treatment. This section explores the primary pathways and modes through which MIF performs all its functions as well as notes that the various actions may change according to the circumstances.

Receptor Binding and Upstream Activation

MIF begins its work by binding with a protein called CD74 which is found within plasma membranes and usually co-clusters with CXCR2, CXCR4, CXCR7. When activated by outside of the cell signals, this receptor multiplex entrusts transcription activation by making JAK2 phosphorylated, bringing in PI3K, and activating Src kinases [11, 13]. MIF behaves as a preformed cytokine; these occurrences are swift and vigorous. MIF-CXCR7 binding turns on the PI3K/AKT pathway in prostate and biliary tract cancers, helping the cancer cells become drug-resistant and divide more rapidly under cytotoxic stress [54, 55]. MIF in the kidney regulates integrin-β1 and cyclin D1 by activating ERK1/2, which helps the kidney cells lose their special function and causes kidney damage [56]. Importantly, MIF engagement with these receptors helps control both inflammation and the survival and repair of cells at the right time.

Core Pathways: PI3K/AKT, NF-κB, and ERK Signaling

Most of the time, receptor binding by MIF causes a chain of events through the PI3K/AKT pathway that supports cell survival, energy use and avoids detection by the immune system. Researchers Wei *et al*. found that exosomes carrying MIF in gliomas make it possible for tumor cells to become resistant to chemotherapy with temozolomide by acting on the TIMP3/PI3K/AKT pathway [57]. MIF also helps preserve the youth of mesenchymal stem cells from ageing due to doxorubicin by using AKT signaling [58]. The p65/p50 arm of NF-κB is an important downstream pathway activated by MIF. In women with PCOS, MIF increases NF-κB activity in granulosa cells, which affects the ovaries and disrupts hormone balance [59]. This mechanism is aided by long non- coding RNA LRNA9884, which increases MIF production by activating NF-κB during acute kidney injury [60]. These signaling cascades act together: ERK1/2 controls cell growth in renal and immune cells, PI3K/AKT helps cells adapt to metabolic changes, and NF-κB maintains inflammation, all showing MIF's ability to influence cellular balance and disease development.

MIF binds to CD74 and co-receptors CXCR2, CXCR4, and CXCR7 to trigger intracellular cascades, such as PI3K/AKT, NF-κB, and MAPK/ERK pathways, as shown in Fig. 3. These signaling pathways control pro-inflammatory cytokine production, resistance to apoptosis, angiogenesis, and immune cell recruitment, leading to tissue repair or chronic inflammation depending on the situation.

Immunomodulation, Inflammation, and Resistance Mechanisms

MIF strongly affects the behavior of immune cells, mainly by influencing the way macrophages are polarized. In adipose tissue, it helps M1 macrophages become active by increasing COX-2 and stops M2 macrophages from becoming active, which causes insulin resistance and ongoing metabolic inflammation [61]. Blocking CD74-MIF signaling has been shown to reverse this polarization, indicating that MIF acts as a molecular switch in inflammatory environments [62]. Beyond innate immune cells, MIF affects T cells, monocytes, and dendritic cells, modulating survival, cytokine secretion, and antigen presentation [63]. It also functions as a counter-regulator of glucocorticoids, antagonizing their anti-inflammatory effects. Genetic variation at the MIF immune susceptibility locus, particularly involving

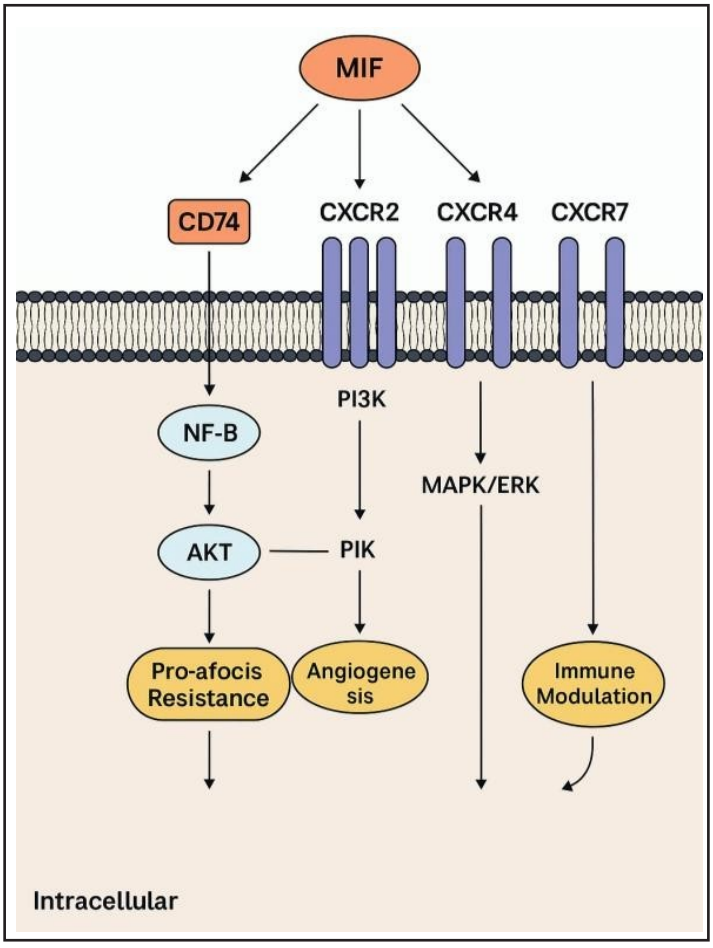

Fig. 3. Receptor-Mediated Signalling Cascades of MIF. MIF binds to CD74 and co-receptors CXCR2, CXCR4, and CXCR7 to trigger intracellular cascades, such as PI3K/AKT, NF-κB, and MAPK/ERK pathways, as shown in Figure 3. These signalling pathways control pro-inflammatory cytokine production, resistance to apoptosis, angiogenesis, and immune cell recruitment, leading to tissue repair or chronic inflammation depending on the situation.

the regulator ICBP90, impacts glucocorticoid sensitivity and apoptosis thresholds [64]. Resistance to therapy, especially in cancers, is reinforced by MIF's integration with non-coding RNAs. For example, microRNA-451a suppresses the MIF-PI3K/AKT pathway in biliary cancers, while its downregulation enables chemoresistance and unchecked proliferation [55]. These interactions underscore the importance of MIF not just in inflammation, but in transcriptional resilience and stress adaptation.

MIF in Cytokine Storms and Systemic Inflammatory States

MIF plays a critical role in the pathogenesis of cytokine storms, particularly in conditions like sepsis, multi-organ failure, and severe viral infections. It is found early in the response, coming before TNF-α and IL-6 increase, and it helps sustain the amount of cytokine mRNA, prolonging the body's systemic inflammation [65]. In this situation, MIF increases the breaking of blood vessels, attracts neutrophils into tissues and damages the endothelium, which are important parts of multi-organ dysfunction syndrome (MODS). MIF also increases COX-2 and PGE2 in tissues other than the brain, which leads to a more general increase in inflammation [66]. Mild inflammation occurs in metabolic disorders; in critical cases, the body responds to danger with immune reactions that do not react to glucocorticoids, which only makes the disease worse [30, 61]. MIF uses both types of immune cells and is not stopped by usual restraints; it allows inflammation to continue, making it a valuable, but difficult, target for therapy.

Role of MIF in Inflammatory Processes

MIF is a main cytokine responsible for organizing the inflammation-related actions of both immune and non-immune cells. It turns on, sustains, and increases inflammation, and it helps the body cope with unexpected stress, although it can also lead to persistent immune issues. In this section, MIF affects macrophage polarization, the development of T-helper and B-cells, the rebuilding of tissues, and the body's inflammatory response, particularly its ability to resist being managed by the immune system.

MIF is well known for shifting macrophages toward the M1 pro-inflammatory type, which increases the secretion of TNF-α, IL-1β, IL-6, and nitric oxide [67]. When the effect is controlled, it helps clear microbes, but when it is out of control, it can harm tissues and lead to autoimmunity [68]. MIF also stops the process by which M2 macrophages differentiate, since these cells help heal and resolve wounds. In detail, MIF helps TLR4 function by keeping it in the membrane and increasing the activation of MyD88-dependent NF- κB, which causes a greater release of cytokines [69]. In marine invertebrate models like *Ciona robusta*, MIF-TLR co-expression during lipopolysaccharide challenge confirms its evolutionarily conserved role in innate immune priming [27]. Importantly, CD74 blockade can reverse this polarization, restoring immune balance and bolstering anti-tumor immunity [70]. Current evidence points to the possibility that MIF interaction with CD74 can be highly regulated by oxidative conditions. In inflamed tissues, where redox imbalance is prevalent, oxidation of MIF seems to drive its conformational modifications and increase receptor binding affinity. This redox-sensitive transition has been suggested as an important initiator of MIF-CD74 interaction and resultant signaling in immune cells. Sajko and group of researches [25] showed that the oxidized state of MIF exhibits modified receptor behavior, which can be used therapeutically to target selectively pathological inflammation. These results crosslink MIF's redox biology and pro-inflammatory function and indicate that oxidative stress not only activates MIF but also enhances it signaling capacity in chronic disease settings.

Modulation of T-Helper Cell Differentiation and Cytokine Imbalance

MIF is important for adaptive immunity, as it mainly controls the T-helper cell subsets' development and function. As a result, there are more Th1 and Th17 cells, which cause inflammation important for diseases such as RA and SLE [30]. MIF stimulates the cultures

of PBMCs and this makes SLE patients release IL-17A, IL-6, and TNF- alpha [71]. The study by Yan and colleagues [72] demonstrated the role of MIF in promoting the differentiation of Th17 cells via promoting the effect of ATF6 signaling pathway connecting endoplasmic reticulum stress to the induction of immune response to unveil an unexpected association between inflammation and endoplasmic reticulum stress. The results show that MIF also assists in the regulation of the inflammatory messages as well as the process of selecting the inflammatory cells.

B Cell Dysregulation and Autoantibody Production

Although studies concentrate more on the effects of MIF on macrophage and T cells, MIF has an effect on B cell biology by aiding the survival and increased numbers of age-related B cells (ABCs). Such cells encompass autoimmune prone and ageing cell populations and produce autoantibodies and secrete cytokines [73]. Phalke with his team [74] explained that there was an accumulation of ABC facilitated by the MIF, which provides a microenvironment, which supports chronic inflammation and presentation of the autoantigens [75]. Sex- and age-dependent variations in the prevalence of autoimmune diseases might also be outlined by this pathway with an increased role of MIF- mediated effect through the modulating influence of estrogen and immune senescence.

MIF in Organ-Specific Inflammatory Pathologies

MIF plays a critical role in the pathogenesis of multiple inflammatory and autoimmune diseases by acting at the interface of immune activation and tissue remodeling. In RA, MIF induces matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), directly contributing to joint erosion and synovial angiogenesis. In SLE, elevated MIF levels correlate with disease activity, particularly nephritis, and reduced response to corticosteroids [76]. In chronic respiratory disorders, MIF promotes leukocyte infiltration and tissue fibrosis, while disrupting barrier function and sustaining a cytokine loop. In these contexts, MIF functions as a non-resolving amplifier, maintaining inflammation even in the absence of active triggers, largely due to its resistance to anti-inflammatory feedback, such as IL-10 or glucocorticoid signaling.

Persistence, Glucocorticoid Resistance, and Transition to Systemic Inflammation

One of the most clinically significant features of MIF is its resistance to classical anti-inflammatory feedback mechanisms. Unlike most cytokines that are downregulated by glucocorticoids, MIF expression is paradoxically upregulated by glucocorticoid signaling, allowing it to bypass immune resolution checkpoints [64]. This trait helps explain MIF's involvement in cytokine storms, where it amplifies systemic inflammation through sustained IL-6 and TNF-α production. Clinically, elevated serum MIF has been linked to a twofold increase in renal flare frequency in SLE and a 30-50% reduction in steroid responsiveness in RA patients [77]. This glucocorticoid resistance, combined with persistent NF-κB activation, establishes MIF as a chronic driver of unresolved inflammation

Immunoregulatory Functions of MIF

In addition to causing inflammation, Macrophage Migration Inhibitory Factor (MIF) plays a role in maintaining balance between tissue repair, tolerance to the immune system, and overall homeostasis. Lymphocytes respond differently to signals in various organs, using CD74 and chemokine receptors and regulate genes using NF-κB, ERK and JNK. Now, investigate the MIF supports the immune system and see that it is beneficial in acute illnesses, but can become problematic if it lasts too long.

Neuroimmune Regulation and Blood-Brain Barrier Dynamics

MIF is involved in both the control of neuroinflammation and the condition of blood vessels in the central nervous system. When ischemic stroke occurs, expression of MIF jumps up, which causes CD74 to be activated and endothelial cell permeability to rise, resulting in damage to the BBB. Liu with colleagues [78] discovered that blocking MIF made the BBB much less leaky and improved outcomes for injured mice. As a result of MIF, more neurons are damaged as RIPK1 activates the death of endothelial cells, which causes more severe harm after a stroke and slower vascular restoration [79]. When MIF is present, it causes microglia to be more active, and this causes an increase in brain cell deaths from cytokines in Alzheimer's disease [80, 13]. Blocking MIF in traumatic brain injury lessens the much astrocytes and lymphocytes that are activated, proving that MIF plays a key role in hyperactive reactions of the brain's immune system [81, 82].

Cardiopulmonary and Hepatic Immune Regulation

During myocardial infarction, the cardiovascular system shows a large increase in MIF, which promotes the activation of cardiac fibroblasts by NF-κB and supports the release of inflammatory cytokines, resulting in poor tissue remodeling [31]. In chronic lung diseases such as pulmonary fibrosis and COPD, MIF contributes to the transformation of lung cells and stops the repair of damage, but it surprisingly also promotes a small amount of new epithelial cell growth [83]. In the liver, MIF acts as a chemokine orchestrator. In alcohol-associated hepatitis, it regulates leukocyte infiltration by coordinating CXCL1 and MCP-1 expression [84]. In contrast, in non-alcoholic steatohepatitis (NASH), MIF promotes fibrosis by shifting NKT cell polarization toward a pro-fibrotic phenotype, rather than resolving inflammation [85]. In hepatocellular carcinoma (HCC), MIF enhances tumor immune evasion by promoting mononuclear phagocyte infiltration, shaping an immunosuppressive microenvironment [86].

MIF in Renal, Gastrointestinal, and Barrier Immunity

In renal tissue, MIF is implicated in both ischemia-reperfusion injury and autoimmune nephritis. It activates tubular epithelial cells and recruits inflammatory macrophages via NF- κB, worsening renal dysfunction [87]. Yang and colleagues [88] demonstrated that macrophage-derived MIF contributes directly to glomerular damage in anti-GBM nephritis. In lupus nephritis models, therapeutic upregulation of miR-654 suppresses MIF and ameliorates renal pathology [89]. In the gastrointestinal tract, MIF supports epithelial cell survival during acute inflammation by promoting CD74-ERK signaling, thereby enhancing mucosal regeneration [90]. However, persistent MIF expression can impair intestinal barrier function, increasing permeability and susceptibility to microbial translocation [91]. In colitis-associated colorectal cancer, MIF orchestrates tumor- promoting interactions between macrophages, T cells, and epithelial cells, fostering chronic immune activation and tumor progression [92].

Metabolic and Reproductive System Immunoregulation

MIF's role in metabolic regulation is increasingly appreciated. It correlates strongly with visceral fat mass, serum hs-CRP, and insulin resistance in prediabetic individuals [93]. It also suppresses hormone-sensitive lipase (HSL) in adipocytes, promoting triglyceride accumulation and adipose inflammation, both key drivers of metabolic syndrome [94]. In the reproductive system, MIF displays a dual function. It promotes trophoblast survival in early pregnancy under oxidative stress by regulating apoptosis and mitochondrial function [95]. Conversely, in endometriosis, elevated serum MIF levels correlate with disease severity and have been proposed as diagnostic biomarkers [96]. In PCOS, MIF activates NF-κB signaling in granulosa cells, exacerbating endocrine dysfunction and ovarian inflammation [59].

Immune Balancing and Therapeutic Relevance

It depends on the environment to either encourage or protect the immune system functions. It is clear from its role as the first messenger in the immune system, its resistance to glucocorticoids, and its effects on both innate and adaptive immunity. MIF can help reduce inflammation in ongoing or cancerous diseases and also support healing and shield tissues under sudden stress. Many of the actions of the inflammatory response are carried out by conserved signaling pathways, NF-κB, ERK1/2, JNK, and CD74-CXCR complexes that are found in many systems but lead to different results in each tissue. That's why targeting MIF in therapy can be tricky, since it helps in many ways and can be harmful if not used the right way. MIF is involved in multifarious physiological functions, and its functional consequences look exceedingly context-specific. In many organ systems, particularly the liver, brain, and reproductive tissues, MIF exhibits protective and harmful activities, contingent upon the stage of disease, the immune environment, and the degree of oxidative stress. For example, MIF ensures epithelial regeneration and tissue repair following acute hepatic insult, but the identical pathway aggravates fibrosis in chronic liver disease. In the CNS and MIF is beneficial to neuroprotection in ischemia, but causes neuroinflammation and neuronal damage in progressive diseases such as Alzheimer's disease. This dualism has been controversial in the literature, with a focus by some studies on its reparative and anti-apoptotic functions, and by others on its role in immune dysregulation and chronic inflammation. These contradictory data highlight the need to take into account tissue specificity, redox status, and disease timing when assessing MIF's mechanistic functions and therapeutic targeting potential.

Clinical Relevance, Diagnostic Potential, and Therapeutic Targeting of MIF

Macrophage Migration Inhibitory Factor (MIF) is now recognized as an important immunoregulatory molecule in many diseases, including autoimmune illnesses, infections, cancers, brain disorders and metabolic problems. The active early, resists glucocorticoid interference and is located upstream in immune responses; it is a good target for precision medicine. In addition to contributing to disease development, MIF is now seen as a helpful marker for diagnosing, predicting outcomes and choosing treatments.

Clinical Significance of MIF in Inflammatory, Oncologic, and Infectious Diseases

In the medical field, MIF is associated with severe, fast, and hard many chronic and acute diseases. In diseases such as RA and SLE, MIF increases inflammation by activating MMPs and makes it harder for glucocorticoids to resolve inflammation, leading to damage in joints and flares throughout the body. Bilsborrow and group of researches [30] pointed out that MIF controls the way macrophages function and supports inflammation in the joints, suggesting it could be a good drug target for RA patients who do not respond to other treatments. In genitourinary cancers, both MIF and its homolog MIF-2 promote growth by acting on the same cancer cells. According to Penticuff and his team [97] high MIF levels in bladder and prostate cancers are linked to a poor outcome and help cancer cells avoid the immune system by recruiting macrophages and promoting blood vessel growth. According to Nasiri and colleagues [80] in Alzheimer's disease, microglial activation and persistent neuroinflammation caused by MIF lead to harm to neurons and cognitive problems. MIF is also implicated in diseases of the blood vessels and metabolism. In atherosclerosis, MIF increases the speed of lesion development by encouraging monocytes to join the lesion and form foam cells [32]. In COVID-19 cases, some variations in the MIF gene have been connected to a higher risk of severe disease. Shin and colleagues [98] found that MIF is a gene linked to COVID-19 outcomes, as high-expression alleles were connected to developing symptoms and problems with the immune system.

MIF's functional consequences in major organs. In the CNS, MIF supports neuroinflammation; in adipose tissue, macrophage-mediated metabolic derangement; in the liver and kidneys, it could cause repair or fibrosis based on disease context. Fig. 4 emphasizes the dual functions of MIF as both a protective and disease-causing mediator.

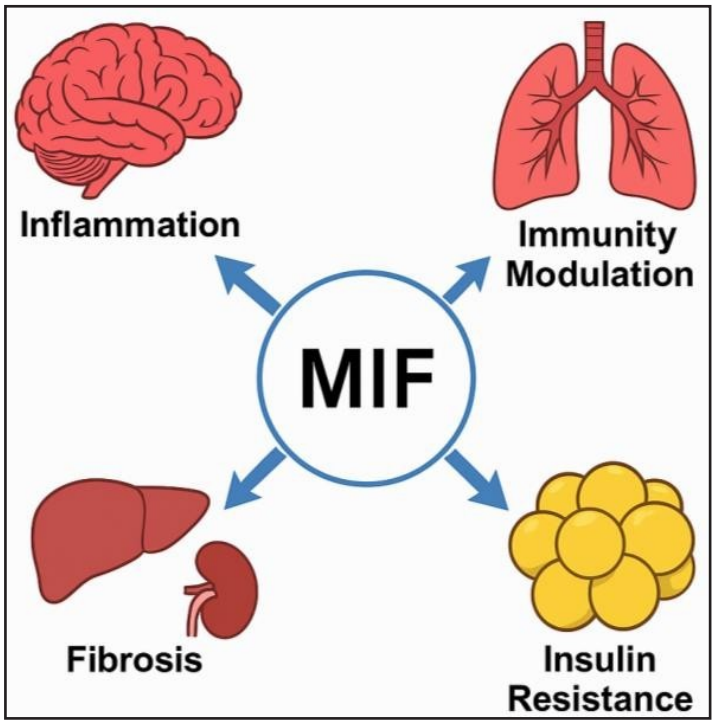

Fig. 4. Organ-Specific Functions of MIF. MIF's functional consequences in major organs. In the CNS, MIF supports neuroinflammation; in adipose tissue, macrophage-mediated metabolic derangement; in the liver and kidneys, it could cause repair or fibrosis based on disease context. Figure 4 emphasises the dual functions of MIF as both a protective and disease-causing mediator.

Diagnostic and Prognostic Utility of MIF and Genetic Markers

Beyond its pathogenic role, MIF demonstrates consistent potential as a quantitative biomarker. High levels of serum MIF, especially above 10 ng/mL, have also been linked with further mortality, multi-organ dysfunction and non-response to therapy in sepsis. Meta-analysis by Toldi *et al* [99]. proved its diagnostic and prognostic properties in a variety of clinical trials and may replace traditional sepsis scores. Serum MIF and soluble CD27 have been noted to be highly sensitive in monitoring the activity of the disease and predicting the relapse in vitiligo [100]. Genetic studies favor the fact that MIF is significant to diagnosis. Gehlen *et al* [101]. revealed that the -173 G>C SNP in the promoter region of MIF is linked to the increased risk of pulmonary tuberculosis among individuals with high rates of MIF expression. In addition to that, the eQTL mapping studies of the lung tissue show that the expression of MIF and MIF-2 is genetically regulated and could play a crucial role in the context of chronic respiratory disorders and the treatment response [102]. The findings show that both the measurement of serum MIF level and genotype testing might contribute to the development of individualized strategies in treating different inflammatory and infectious conditions.

Advances in Therapeutic Targeting of MIF and MIF-2

MIF treatment is done by therapists through three primary modes, and these include small- molecule medicines, CD74 blockers, and gene or antibody-based therapies. There are two inhibitors, ISO-1 and MIF-2, that were developed in a laboratory and are likely to prevent the work of tautomerase, as well as the work of the receptor proteins. Tilstam *et al* [53]. discovered that when MIF-2 is prevented from forming, inflammation is reduced, but MIF still contributes to tissue healing. The presence of MIF and MIF-2, and their receptors, helps improve the treatment carried out [103]. Working on the MIF-CD74 connection has been beneficial. Chan and his team found that decreasing CD74 in mice with obesity decreased the activity of M1 macrophages, improved insulin function, and lowered inflammation in fat cells, showing that MIF signaling affects metabolic problems [104]. Precision immunotherapy is also using CRISPR, RNA interference, and monoclonal antibodies to lower the amount or

activity of MIF. Kang and Bucala [6] believe that testing for MIF polymorphisms in patients may improve treatment outcomes, mainly in autoimmune and cancer diseases where MIF levels are not properly regulated [105]. At this point, scientists are testing the safety of these treatments to develop ones that can treat chronic inflammation early and have fewer negative effects on the immune system. Aside from agents mentioned previously, more diverse sets of therapeutic approaches have since been created to target MIF family proteins. Orthosteric inhibitors function by directly interacting within the catalytic tautomerase pocket, usually through the conserved Pro1 residue, thus inhibiting receptor interaction. Conversely, allosteric modulators, including Iguratimod and other solvent channel blockers, act by changing the conformation of MIF and not by filling its active site, providing greater selectivity with potentially fewer side effects. Covalent inhibitors also exist, which bind irreversibly to crucial residues to provide prolonged inhibition, especially in situations of chronic inflammation. Notably, the therapeutic strategies now segregate by MIF and structural homolog MIF-2, their distinct receptor binding and tissue-restricted functions having been appreciated. Selective MIF-2 inhibitors have exhibited anti-inflammatory effects in multiple autoimmune and metabolic disease models, underscoring the value of isoform-specific pharmacological logic. This larger pharmacological repertoire offers a richer landscape to interfere with MIF-mediated pathologies and optimize interventions to the disease context and expression profile.

Future Directions

Although important advances have been made in defining the functions of MIF and MIF-2 in immune regulation, inflammation, and disease, several key questions have to be addressed. At a structural level, the absence of high-resolution structures of MIF-receptor complexes, especially with CD74 and CXCR co-receptors, restricts knowledge regarding specific binding interfaces and receptor recognition-induced conformational changes. Mechanistically, the functional effects of MIF oxidation, dimerization status, and intracellular partner interactions like with JAB1 and CSN5 remain to be fully understood. Therapeutically, while a number of small-molecule and monoclonal antibody inhibitors of MIF have exhibited preclinical potential, there are issues regarding the attainment of isoform specificity, off-target effects, and overcoming immune compensation. The dual role of MIF, being protective in acute responses and pathogenic in chronic inflammation, represents a major obstacle for developing broadly effective therapies. The future will focus on the following important areas: definition of tissue- and context-dependent MIF functions through spatial transcriptomics and proteomics, the development of targeted delivery platforms to selectively modulate MIF activity in diseased tissues, and clarification of the genetic polymorphisms or post-translational modifications that will be known to impact MIF function across different patient groups. Resolution of these issues will further improve the translational potential of MIF-targeted therapies and define its utility as a biomarker in personalized medicine.

Conclusion

Macrophage Migration Inhibitory Factor (MIF) has evolved from a historically defined cytokine into a multifunctional immune regulator with profound relevance across physiology and pathology. This review has explained that MIF is active at the meeting point of innate and adaptive immunity, affecting many processes by signaling through CD74, CXCR4/7 and leading to the activation of NF-κB, ERK1/2, PI3K/AKT, and JNK. It is not easily suppressed by glucocorticoids; it acts as a major cause of inflammation in both sudden and long-lasting conditions. At the cellular level, MIF governs macrophage polarization, favors Th1 and Th17 lineage differentiation, sustains B cell hyperactivation, and contributes to immune evasion in cancer. These mechanisms have wide-reaching consequences in autoimmune disorders (RA,

SLE), metabolic dysfunction (obesity, insulin resistance), chronic inflammatory diseases (asthma, hepatitis, nephritis), and neurodegeneration (Alzheimer's disease, ischemic stroke). MIF's context-dependent duality, protective in controlled injury but pathogenic in unresolved inflammation, makes it a complex but crucial modulator of tissue microenvironments. Importantly, integrating MIF polymorphisms, serum level monitoring, and tissue-specific expression patterns has paved the way for its use as a diagnostic and prognostic biomarker. Elevated MIF levels have been linked to disease severity, therapeutic resistance, and relapse risk in diverse disorders, including sepsis, tuberculosis, COVID-19, vitiligo, and cancers. Genotype-phenotype associations have further demonstrated that the individual MIF expression profiles can influence susceptibility and response to treatment, advancing its utility in precision medicine. Therapeutically, MIF has become a viable intervention point for targeted drug development. Strategies such as small-molecule inhibitors, MIF-2-selective blockers, CD74 antagonists, and gene-editing tools (e.g., RNAi, CRISPR) are being investigated for their ability to neutralize MIF activity without compromising protective immune functions. These approaches have shown promise in preclinical models of inflammatory, metabolic, oncologic, and fibrotic diseases. However, the therapeutic challenge remains to discriminate pathological MIF signaling from its physiological roles in tissue protection, regeneration, and acute immune defense. MIF stands at the forefront of immunopathology as a dynamic cytokine with diagnostic, prognostic, and therapeutic value. Its capacity to influence inflammation, immunity, metabolism, and cellular resilience across organ systems makes it a central hub in disease modulation. Future translational efforts must focus on integrating MIF-targeting strategies into patient-specific frameworks, leveraging biomarker intelligence and genetic profiling to refine efficacy and safety. With its multidimensional role now firmly established, MIF represents not only a therapeutic target but also a paradigm for immunological systems biology in the era of precision healthcare.

Disclosure Statement

The authors have nothing to disclose.

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