Molecular mechanisms of macrophage migration inhibitory factor in related diseases (Review)

LIPING CHEN[1], XINYI KANG[1], XUEQIN ZOU[1], GENGSHENG WANG[1], QIUKAI E.[1] and CHONGXU SHI[2]

[1]Department of Obstetrics and Gynecology, Nantong First People's Hospital, Southeast University, Nantong Clinical College, Nantong University, Nantong, Jiangsu 226001, P.R. China; [2]Nantong Laboratory of Development and Diseases, School of Life Science, Nantong University, Nantong, Jiangsu 226001, P.R. China

Received May 11, 2026; Accepted August 14, 2026

DOI: 10.3892/br.2026.2197

Abstract. Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that exerts dual-faced, context-dependent roles in physiological and pathological processes. While it maintains tissue homeostasis and facilitates repair under normal conditions, MIF acts as a 'double-edged sword' following tissue injury. As a primary initiator of early inflammatory responses, MIF regulates immune cell activation, oxidative stress, and downstream inflammatory cascades. The present review focuses on the molecular mechanisms and therapeutic potential of MIF signaling in three critical inflammation-related conditions: Cerebral infarction, atherosclerosis, and acute kidney injury. It is first delineated how MIF signaling pathways drive disease progression or protection. Furthermore, recent advancements in MIF-targeted therapies are summarized, and the intricate regulatory factors, including dosage, timing, and microenvironmental cues, that govern its bifunctional nature are examined. By highlighting current clinical challenges and prospects, the present review underscores the potential of MIF as a precise therapeutic target for systemic inflammatory diseases.

Contents

Correspondence to: Dr Chongxu Shi, Nantong Laboratory of Development and Diseases, School of Life Science, Nantong University, 9 Seyuan Road, Nantong, Jiangsu 226001, P.R. China
E-mail: chongxu.shi@gmail.com; shicx202112@ntu.edu.cn

Dr Liping Chen, Department of Obstetrics and Gynecology, Nantong First People's Hospital, Southeast University, Nantong Clinical College, Nantong University, 666 Shengli Road, Nantong, Jiangsu 226001, P.R. China
E-mail: jichen0816@163.com

Key words: macrophage migration inhibitory factor, inflammation, immune response, targeting therapy

1. Overview of MIF

Macrophage migration inhibitory factor (MIF) is a versatile, pleiotropic cytokine that serves as a central orchestrator of complex signaling networks by interacting with multiple cell-surface receptors. Under physiological conditions, constitutively expressed MIF acts as a homeostatic guardian, modulating cell survival, immune surveillance, and oxidative stress response (1).

The biological activity of MIF is primarily mediated by multi-component receptor complexes, with the type II transmembrane protein cluster of differentiation 74 (CD74) serving as the primary ligand-binding subunit (2,3). Canonical signaling complexes include CD74/CD44, CD74/C-X-C motif chemokine receptor 2 (CXCR2), CD74/C-X-C motif chemokine receptor 4 (CXCR4), and the more recently identified CD74/CXCR4/C-X-C motif chemokine receptor 7 (CXCR7) trimeric complex (4). Depletion of CD74 has been shown to significantly impair MIF-mediated biological processes, such as inflammatory cytokine release and cell proliferation, even in the presence of other co-receptors such as CXCR2 or CXCR4 (5). Beyond CD74-dependent pathways, MIF can signal independently. For instance, it can trigger the phosphoinositide 3-kinase (PI3K) survival pathway through direct engagement with the CXCR7 receptor alone (3). Furthermore, proteolytic cleavage of CD74 liberates its intracellular domain (CD74-ICD), which translocates to the nucleus to activate nuclear factor-κB (NF-κB), ultimately governing downstream programmed cell death pathways and inflammatory gene expression (3).

In pathological processes, MIF acts as a key initiator, sustaining and amplifying acute and chronic inflammatory cascades by coordinating immune cell activation and recruitment (6,7). Furthermore, it mediates cellular responses to oxidative damage, particularly in sensitive tissues such as the brain and kidneys (8,9). Given its central role in cerebral infarction, atherosclerosis, and acute kidney injury (AKI), MIF has emerged as a highly promising therapeutic target.

Understanding the delicate balance between its homeostatic physiology and pathogenetic driver effects is essential for developing precise targeted interventions.

2. Literature search and study selection

To systematically synthesize existing literature, an extensive database search was performed using PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/). The retrieval strategy combined target keywords, including 'Macrophage Migration Inhibitory Factor', 'MIF', 'CD74', 'CXCR2', 'CXCR4', 'cerebral infarction', 'ischemic stroke', 'atherosclerosis', 'acute kidney injury', 'AKI', 'ISO-1', and 'MIF polymorphisms'. Eligible studies comprised peer-reviewed original articles, meta-analyses, and comprehensive reviews focused on the molecular mechanisms, receptor signaling, and therapeutic targeting of MIF in neurovascular, cardiovascular, and renal pathologies, alongside preclinical *in vivo* and *in vitro* functional evaluations published in English. Conversely, non-peer-reviewed preprints, conference proceedings, editorial materials, retracted papers, duplicate records, and studies devoid of clear mechanistic context were excluded. Given the context-dependent biology of MIF, divergent experimental findings were critically resolved by stratifying studies according to disease stage (acute vs. chronic/repair phases), genetic models (conditional cell-specific knockout vs. global deficiency or pharmacological blockade), and the exposure dynamics (dosage and kinetics) of MIF modulators.

3. Mechanism and therapeutic prospects of MIF in related diseases

MIF in cerebral infarction. Cerebral infarction, commonly referred to as ischemic stroke, results from sudden obstruction of cerebral blood circulation. This blockage causes rapid ischemic damage, tissue necrosis, and neurological deficits such as paralysis and aphasia (10,11). Ischemic injury triggers an acute inflammatory cascade characterized by leukocyte infiltration and the release of pro-inflammatory cytokines, which together drive secondary brain injury, cerebral edema, and infarct expansion (12,13). Furthermore, severe metabolic impairments drive the overgeneration of reactive oxygen species (ROS), accelerating mitochondrial dysfunction and programmed neuronal death (14).

MIF is a central regulator in post-stroke neuroinflammation and cell fate decision (15,16). Clinical evidence has revealed that acute ischemic stroke triggers a marked upregulation of both MIF and its primary receptor, cluster of differentiation 74 (CD74), which is directly associated with stroke severity. Certain stroke models using *Mif*-deficient ($Mif^{-/-}$) mice have shown that baseline pro-inflammatory cytokines and CD74 levels remain unaffected, indicating potential compensatory mechanisms (such as C-X-C motif chemokine ligand 12 (CXCL12)/CXCR4 signaling) (12). Ligand binding to the CD74 receptor complex was found to initiate mitogen-activated protein kinase (MAPK) signaling, mobilizing peripheral monocytes and macrophages into the ischemic lesion (17,18). Crucially, hypoxia-induced MIF expression was demonstrated to promote endothelial cell autophagy, triggering the autophagic degradation of tight junctions (19,20). This breakdown was shown to compromise blood-brain barrier (BBB) integrity, worsening vasogenic edema, intracranial hypertension, and tissue necrosis (19-21).

Paradoxically, MIF also exhibits profound neuroprotective effects within the vulnerable ischemic penumbra (16,19). Mechanistically, intracellular MIF directly engages Jun activation domain-binding protein 1 (Jab1) (20,22). Under cellular stress, free Jab1 functions as a co-activator of c-Jun N-terminal kinase (JNK) signaling; by binding Jab1, MIF suppresses JNK hyperactivation, thereby curbing stress-induced apoptotic pathways (20,22). In addition, MIF limits neuronal loss by downregulating the pro-apoptotic transcription factor p53 and promoting the expression of brain-derived neurotrophic factor (BDNF), a vital neurotrophin for synaptic plasticity and cell survival (23-26).

Because penumbral apoptosis is potentially reversible, salvaging cells in this region is a primary clinical objective (27,28). The small-molecule MIF inhibitor, (S, R)-3-(4-Hydroxyphenyl)-4,5-dihydro-5-isoxazole methyl acetate (ISO-1) has demonstrated promising neuroprotective efficacy (29). By blocking mitochondrial apoptotic proteins in the penumbra and restoring endothelial tight junction integrity, ISO-1 has been shown to preserve BBB function and mitigate neurological deficits (21,29). Collectively, these findings highlight the fine-tuned modulation of MIF as a viable therapeutic strategy for ischemic cerebral infarction.

MIF in atherosclerosis. Atherosclerosis is a chronic, progressive inflammatory disorder of large and medium-sized arteries, initiated by the subendothelial deposition of cholesterol-rich complexes (30,31). This localized lipid retention triggers a self-amplifying 'lipid-inflammatory loop', wherein non-resolving immune cascades accelerate structural vascular remodeling (30-32).

In early atherogenesis, activated or injured endothelial cells upregulate cell adhesion molecules, facilitating the rolling, arrest and transendothelial migration of circulating monocytes into the arterial intima (30). Within the subendothelial space, these monocytes differentiate into macrophages, which engulf modified low-density lipoproteins (LDL) and transform into cholesterol-laden foam cells (31). Massive foam cell accumulation fuels a robust pro-inflammatory milieu, recruiting secondary immune cells and stimulating vascular smooth muscle cell (SMC) migration and proliferation (32). Recruited SMCs synthesize extracellular matrix proteins to form a protective fibrous cap over a necrotic core composed of apoptotic foam cells and lipid debris (32,33). In advanced lesions, cholesterol crystallization, matrix degradation, and microvascular calcification drive fibrous cap thinning and plaque vulnerability; plaque rupture exposes highly thrombogenic core material to circulating blood, precipitating acute vascular occlusion, myocardial infarction, or stroke (33).

MIF expression levels are closely associated with the clinical progression of atherosclerosis (34). Under physiological conditions, baseline MIF expression remains low in resting endothelial cells and SMCs (34). During early adaptive intimal thickening, MIF expression increases, signaling its involvement in early vascular remodeling (34). As lesions transition into active inflammatory plaques,

MIF surges within foam cells, macrophages, SMCs, and T lymphocytes (34). Mechanistically, MIF interacts with the transcriptional coactivator Jab1 to activate activator protein-1 (AP-1), amplifying downstream inflammatory gene expression (34). In advanced vulnerable plaques, MIF is heavily enriched within the expanding necrotic core (34). A defining feature of MIF in atherosclerosis is its non-canonical function as an 'adhesion chemokine' (35). MIF directly binds to the chemokine receptors CXCR2 and CXCR4 alongside CD74, inducing intracellular calcium (Ca^{2+}) influx and activating αLβ2 and α4β1 integrins on monocytes (35,36). MIF upregulates vscular cell adhesion molecule 1 (VCAM-1) and intercellular adhsion molecule 1 (ICAM-1) expression while stimulating C-C motif chemokine ligand 2 (CCL2) production, together activating macrophage arrest and transmigration into the plaque (37,38). Once inside the lesion, MIF promotes unregulated LDL uptake and drives the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β (37,39). Moreover, MIF upregulates matrix metalloproteinases (MMPs), which degrade collagen fibers within the fibrous cap, accelerating plaque destabilization (39,40). Beyond intra-plaque inflammation, MIF serves as a platelet-derived chemokine that regulates local thrombotic responses following endothelial erosion or rupture (41).

Given its multifaceted role in driving monocyte recruitment, foam cell formation, cytokine cascades, and fibrous cap thinning, MIF represents a high-value therapeutic target (35,37,40). In preclinical mouse models, adenovirus-mediated *Mif RNA* interference or neutralizing anti-MIF antibodies markedly suppressed aortic inflammation, reduced lipid and macrophage deposition, and promoted the regression of established plaques (42,43). Therapeutic inhibition of MIF activity has been shown to stabilize atherosclerotic lesions by shrinking necrotic cores, reducing foam cell counts, and preserving stabilizing SMC coverage (35). Collectively, precision strategies designed to selectively disrupt atherogenic MIF signaling hold significant potential for cardiovascular and peripheral vascular diseases.

MIF in AKI. AKI is a complex clinical syndrome characterized by a rapid decline in renal function over hours or days. Clinically, AKI is diagnosed according to KDIGO criteria, defined by an absolute increase in serum creatinine of higher than 0.3 mg/dl (26.5 μmol/l) within 48 h, a 50% rise from baseline within 7 days, or a sustained reduction in urine output to <0.5 ml/kg/h for at least 6 h. AKI represents a major global health challenge, affecting over 20% of hospitalized patients and >50% of critically ill patients in intensive care units. Beyond the acute phase, AKI is a critical risk factor for the development of chronic kidney disease (CKD) and end-stage kidney disease, carrying high long-term morbidity (with a CKD transition rate of 25-43%) and mortality rates (with 1 and 5-year post-discharge mortality reaching up to 28 and 40%, respectively) (44).

In the healthy kidney, MIF is constitutively expressed across various cell types, including glomerular podocytes, mesangial cells, tubular epithelial cells, fibroblasts, and leukocytes (45). Upon renal insult, MIF is rapidly released from damaged renal tubular epithelial cells, as well as infiltrating immune and vascular cells, to serve as a proximal driver of local inflammatory cascades (46). Under severe ischemic, toxic, or septic stress, hypersecreted MIF engages CD74 and CXCR2/CXCR4 receptor complexes, triggering the expression of key pro-inflammatory mediators [TNF-α, IL-1β, and monocyte chemoattractant protein-1 (MCP-1)] and infiltrating neutrophils, macrophages, and T cells into the tubulointerstitium (47). Mechanistically, MIF binds to vimentin to assemble and activate the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, accelerating caspase-1 cleavage and the release of pro-inflammatory cytokines IL-1β and IL-18, which drive tubular cell pyroptosis and renal injury expansion (48,49).

The role of MIF in AKI is multifaceted, context-dependent, and governed by its local concentration, disease phase, and tissue microenvironment (8). During the recovery and repair phase, MIF acts as an essential survival factor (8). Through its intrinsic thiol-protein oxidoreductase activity, MIF quenches ROS, enhances glutathione synthesis, and inhibits lipid peroxidation, thereby limiting tubular necrosis (48,50). In ischemia-reperfusion models, MIF has been shown to promote tubular epithelial cell regeneration, prevent tubular cell cycle arrest, and mitigate subsequent renal fibrosis (47,48,50,51). Consequently, *Mif* gene deletion often leads to exacerbated overall tissue destruction and impaired tubular regeneration (8,52).

Targeting the MIF signaling pathway offers promising therapeutic avenues for AKI management. The catalytic MIF inhibitor ISO-1 was found to markedly prevent NLRP3 inflammasome activation, attenuate pro-inflammatory cytokine expression, and reduce pathological tubular damage in preclinical AKI models (48,53). Ribosomal protein S19 (RPS19), released by apoptotic cells during tissue turnover, functions as a crucial endogenous checkpoint (54). RPS19 directly binds extracellular MIF to block its receptor-binding interface, thereby halting downstream NF-κB activation and driving resolution of cisplatin-induced AKI (51). Human pharmacogenetic studies have demonstrated that functional promoter variants in the *MIF* gene, such as the 173G/C (rs755622, single-nucleotide polymorphism) and the rs3063368, predict increased susceptibility to AKI (such as post-cardiac surgery), heightened post-operative mortality, and accelerated progression from AKI to CKD (45,51,52,55,56).

In summary, MIF is a pivotal yet multifaceted orchestrator in AKI pathophysiology. While its acute hypersecretion drives destructive inflammation and pyroptosis, its baseline and late-phase signaling support redox balance and tubular repair. Delineating the precise therapeutic window, dosage kinetics, and patient-specific genetic profiles will be essential for successfully translating MIF-targeted therapies into clinical practice.

4. Discussion

Divergent molecular mechanisms across disease contexts. The biological impact of MIF is dictated by its interaction with a diverse array of membrane receptors and intracellular partners, leading to distinct outcomes across cerebral, cardiovascular, and renal pathologies (Fig. 1). In atherosclerosis, MIF

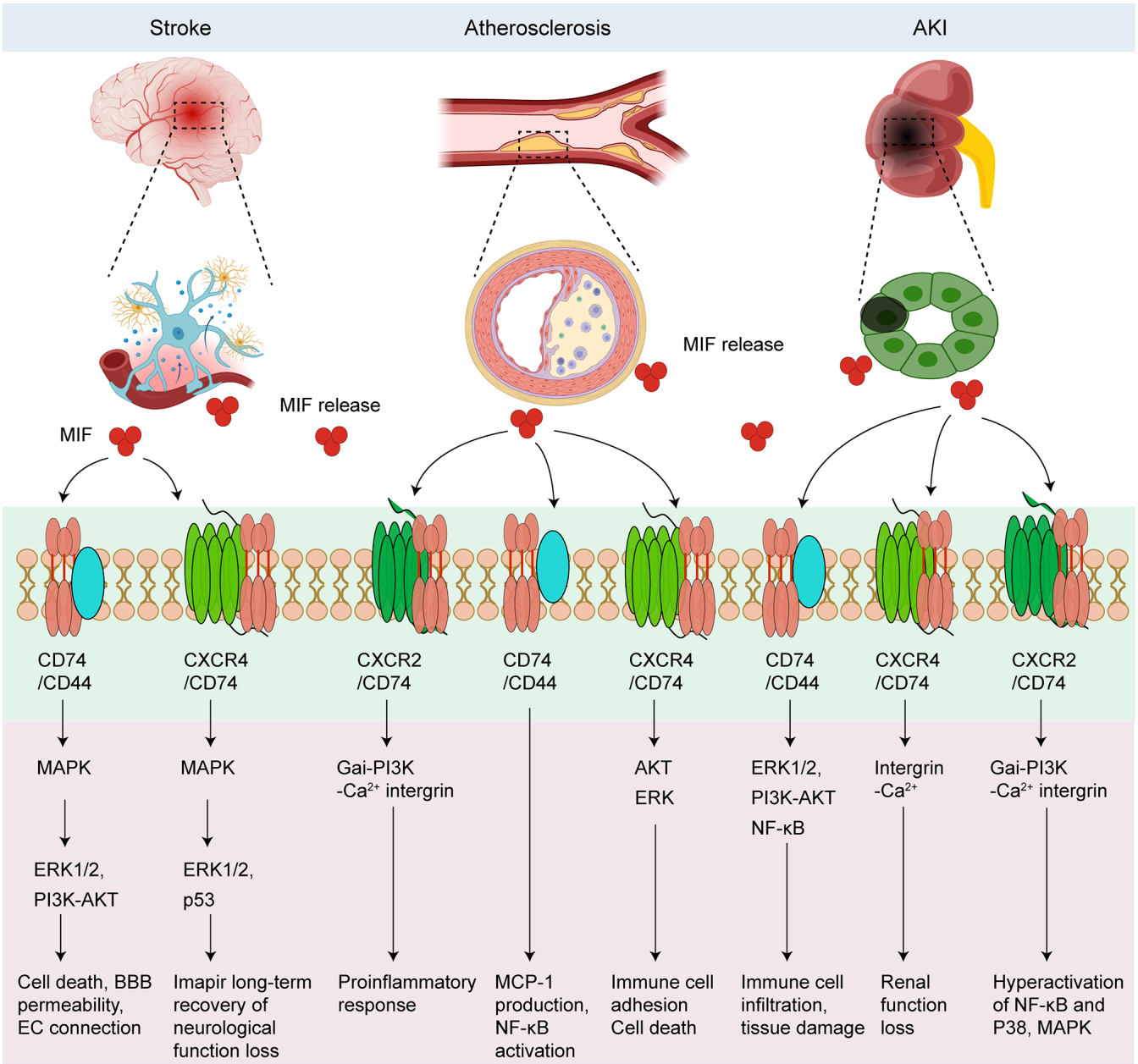

Figure 1. MIF receptor signaling across stroke, atherosclerosis, and AKI. Stroke: Extracellular MIF engages CD74/CD44 and CXCR4/CD74 complexes to activate MAPK/ERK, PI3K-AKT, and p53 signaling, promoting endothelial connection disruption, BBB hyperpermeability, cell death, and impairment of neurological recovery. Atherosclerosis: MIF signals through CXCR2/CD74, CD74/CD44, and CXCR4/CD74 to stimulate Ga_i-PI3K-Ca^{2+}-integrin, MCP-1/NF-κB, and AKT/ERK pathways, driving pro-inflammatory responses, immune cell adhesion, and cell death. AKI: Interaction of MIF with CD74/CD44, CXCR4/CD74, and CXCR2/CD74 activates NF-κB, MAPKs (p38/ERK), and Ca^{2+}-integrin signaling, promoting immune cell infiltration, tissue damage, and renal function loss. MIF, macrophage migration inhibitory factor; AKI, acute kidney injury; CD74, cluster of differentiation 74; CD44, cluster of differentiation 44; CXCR4, C-X-C motif chemokine receptor 4; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; p53, tumor protein p53; BBB, blood-brain barrier; CXCR2, C-X-C motif chemokine receptor 2; Gαi, G protein αi subunit; Ca^{2+}, calcium ion; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB.

primarily dictates leukocyte recruitment and vascular homeostasis via the CXCR4 and CCL2 pathways. The MIF-CXCR4 axis typically exacerbates plaque inflammation by recruiting leukocytes into the subendothelial space (57). MIF simultaneously coordinates with CCL2 in SMCs to maintain macrophage homeostasis, potentially limiting chronic inflammation under certain microenvironmental conditions (58).

Renal MIF signaling is mediated by the CD74-NF-κB, PTEN-induced putative kinase 1 (PINK1), and AMP-acitvated protein kinase (AMPK) pathways (41,52-54). In sepsis or cisplatin-induced AKI, MIF engages CD74-NF-κB to amplify the inflammatory response and induce tubular cell pyroptosis through NLRP3 activation (59,60). Furthermore, intracellular binding of MIF to PINK1 inhibits mitophagy, leading to toxic ROS accumulation (61). Conversely, in ischemia-reperfusion models, MIF was shown to activate the AMPK pathway to upregulate antioxidant defenses, thereby inhibiting ferroptosis and protecting tubular integrity (46).

In cerebral ischemia, MIF signaling exhibits profound complexity. Beyond compromising BBB integrity, MIF

directly interacts with apoptosis-inducing factor (AIF) to form a pro-apoptotic complex, which promotes AIF nuclear translocation, driving chromatin condensation, DNA fragmentation, and progressive neuronal death (19,62).

Regulatory factors governing the 'double-edged sword'. The functional transition of MIF from a protective to a lethal factor is influenced by dosage, timing, post-translational modifications, and host microenvironments.

In cerebral infarction, high-dose intravenous MIF (3.3 μg/kg) exacerbates BBB disruption and expands infarct size, whereas a low-dose intraventricular injection (120 ng/ml) provides neuroprotective effects, underscoring an extremely narrow therapeutic window (16,19). Molecular modifications can fundamentally alter MIF function. For example, aspirin-mediated acetylation at the MIF-K78 site physically prevents its interaction with AIF, thereby reducing neuronal apoptosis (62). In the progression of atherosclerosis, the vascular protective effect of *Mif* gene deletion is prominent in younger mice but diminishes with age, suggesting that the systemic inflammatory environment matures (37,58,63). Similarly, in AKI, MIF acts as an essential survival signal during I/R injury via the AMPK-glutathione redox axis, whereas it converts into a destructive inflammatory driver during toxic insults (such as cisplatin) by driving NF-κB-mediated cytokine storms (46,59).

Clinical challenges and prospects of MIF-targeted therapy. Despite promising preclinical efficacy of inhibitors such as ISO-1, translating MIF-targeted therapies into clinical practice faces significant translational hurdles. In stroke, the CXCR4 antagonist AMD3100 suppresses microglial overactivation, while the CXCR7 agonist VUF11207 reduces inflammatory infiltration by limiting platelet activation (64,65). However, the restricted dose-dependent paradox and narrow administration windows hamper safe clinical trial design. Precisely tuning MIF receptor pathways without compromising baseline neuroprotective functions remains a formidable challenge. In atherosclerosis, targeting the CD74 pathway, either through cathepsin S inhibition or CD74 siRNA, has shown promise in reducing plaque size and stabilizing the vascular environment (66-68). Nevertheless, key hurdles persist, including achieving targeted *in vivo* gene silencing and navigating the cell-type-specific functional diversity of receptors such as CXCR7, which complicates the selective inhibition of pathological processes without disrupting physiological functions. In AKI, antagonists such as repertaxin (CXCR2) and plerixafor (CXCR4) have demonstrated the ability to attenuate tubulointerstitial damage and vascular leakage in AKI models (69,70). Yet, because low-level MIF signaling is indispensable for tubular cell regeneration and tissue homeostasis, long-term or systemic MIF blockade risks impairing intrinsic renal repair mechanisms.

Limitations of current evidence. While accumulated experimental data highlight MIF as a key driver and therapeutic candidate in cerebral, cardiovascular, and renal pathology, several critical limitations in the current evidence base must be acknowledged. Primarily, current mechanistic and therapeutic insights for MIF modulation rely on *in vitro* and animal model studies, with a absence of well-designed, large-scale human clinical trials evaluating direct MIF inhibitors or receptor-targeted biologics. Experimental heterogeneity across animal species, genetic backgrounds, and injury protocols generates divergent findings, while global *Mif* knockout models often trigger compensatory developmental adaptations (such as rewired chemokine networks) that mask the genuine acute outcomes of therapeutic MIF inhibition.

Furthermore, an incomplete understanding of receptor-specific MIF signaling poses a major mechanistic challenge. MIF operates within a complex receptor matrix (CD74, CXCR2, CXCR4, and CXCR7) capable of multimeric heterocomplex assembly. How receptor availability, cell-surface dynamics, tissue-specific expression, and ligand-biased signaling modulate distinct or opposing cell fate decisions across different disease microenvironments is yet to be fully elucidated.

Finally, translational barriers impede the clinical application of MIF-targeted interventions. Developing safe human therapeutics requires precise navigation of the narrow therapeutic window of MIF, balancing the preservation of beneficial baseline/repair signaling with the suppression of harmful acute hypersecretion, while avoiding off-target toxicities or impaired tissue regeneration. Additionally, despite established associations between specific MIF promoter variants [such as -173G/C (rs755622) and -794 CATT5-8 (rs3063368)] and disease risk, extensive longitudinal studies validating circulating MIF levels or precision genotype-guided patient stratification in clinical practice remain scarce.

5. Conclusion and future directions

MIF serves as a central orchestrator of innate immunity and tissue repair, profoundly influencing the trajectory of cerebral, cardiovascular, and renal pathologies. Far from being a simple pro-inflammatory mediator, MIF functions as a context-dependent 'double-edged sword' whose biological impact is strictly governed by its local concentration, release kinetics, and microenvironment-specific receptor interactions. While low-level signaling is essential for redox balance and physiological cell survival, hypersecretion drives unchecked inflammatory cascades and tissue necrosis.

Despite the compelling efficacy of small-molecule inhibitors (such as ISO-1) and receptor antagonists in preclinical models, translational progress remains constrained by two fundamental hurdles. First, due to the broad functional pleiotropy of MIF, unselective systemic blockade risks disrupting indispensable homeostatic repair processes. Second, the marked 'dose-response' paradox, where high doses exacerbate damage while micro-doses confer protection, defines an exceptionally narrow therapeutic window that severely complicates clinical protocol design.

To overcome these translation barriers, future research must shift from global inhibition toward high-precision modulation. Priority should be given to mapping spatiotemporal timing thresholds, developing cell-type-specific receptor antagonists, and exploiting post-translational modifications (such as site-specific acetylation) to selectively silence pathological cascades while sparing tissue repair. Ultimately, integrating systems-biology frameworks with functional pharmacogenetics (such as MIF-173G/C profiling) will be essential

to establish safe, personalized therapies for diverse ischemic and inflammatory disorders.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Open Project of Jiangsu Province Science and Technology Resources (Major Disease Biological Samples) Integrated Service Platform (grant no. TC2022B019), the Science Foundation of Kangda College of Nanjing Medical University (grant no. KD2024KYJJ290), the Scientific Research Project of Nantong Municipal Health Commission (grant no. QNZ2022007), the Special Clinical Medicine Project of Nantong University (grant no. 2023JQ001), the Project of Nantong Municipal Health Commission (grant no. QNZ2023031), and the Nantong Science and Technology Bureau (grant nos. MS2024036, MS2025052 and JC2025065).

Availability of data and materials

Not applicable.

Authors' contributions

LC and XK drafted the original manuscript. XZ, GW and QE participated in the manuscript revision. CS and LC helped acquire funding and designed the review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Google Gemini) were used to improve the readability and language of the manuscript, 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.

References

1. Camacho Meza G, Avalos Navarro G, De La Cruz Mosso U, Ramírez Patiño R, Muñoz Valle JF and Bautista Herrera LA: Macrophage migration inhibitory factor: Exploring physiological roles and comparing health benefits against oncogenic and autoimmune risks (review). Int J Mol Med 56: 149, 2025.
2. Zhang L, Woltering I, Holzner M, Brandhofer M, Schaefer CC, Bushati G, Ebert S, Yang B, Muenchhoff M, Hellmuth JC, *et al*: CD74 is a functional MIF receptor on activated CD4$^+$ T cells. Cell Mol Life Sci 81: 296, 2024.
3. Tanese K and Ogata D: The role of macrophage migration inhibitory factor family and CD74 in the pathogenesis of melanoma. Exp Dermatol 33: e15122, 2024.
4. Jankauskas SS, Wong DWL, Bucala R, Djudjaj S and Boor P: Evolving complexity of MIF signaling. Cell Signal 57: 76-88, 2019.
5. Khezrian A, Shojaeian A, Khaghani Boroujeni A and Amini R: Therapeutic opportunities in breast cancer by targeting macrophage migration inhibitory factor as a pleiotropic cytokine. Breast Cancer (Auckl) 18: 11782234241276310, 2024.
6. Lang T, Lee JPW, Elgass K, Pinar AA, Tate MD, Aitken EH, Fan H, Creed SJ, Deen NS, Traore DAK, *et al*: Macrophage migration inhibitory factor is required for NLRP3 inflammasome activation. Nat Commun 9: 2223, 2018.
7. Youness RA, Elemam NM, Abdelhamid AM, Mohamed AH, Elsherbiny LM, Ramzy A and Assal RA: Macrophage migration inhibitory factor (MIF) and the tumor ecosystem: A tale of inflammation, immune escape, and tumor growth. Front Immunol 16: 1636839, 2025.
8. Kong YZ, Chen Q and Lan HY: Macrophage migration inhibitory factor (MIF) as a stress molecule in renal inflammation. Int J Mol Sci 23: 4908, 2022.
9. Yukitake H, Takizawa M and Kimura H: Macrophage migration inhibitory factor as an emerging drug target to regulate antioxidant response element system. Oxid Med Cell Longev 2017: 8584930, 2017.
10. Yin Q and Yang L: Mechanisms of cognitive impairment associated with cerebral infarction. Zhong Nan Da Xue Xue Bao Yi Xue Ban 49: 1692-1699, 2024 (In English, Chinese).
11. Lee JM, Zipfel GJ and Choi DW: The changing landscape of ischaemic brain injury mechanisms. Nature 399 (6738 Suppl): A7-A14, 1999.
12. Emerich DF, Dean RL III and Bartus RT: The role of leukocytes following cerebral ischemia: Pathogenic variable or bystander reaction to emerging infarct? Exp Neurol 173: 168-181, 2002.
13. Shichita T, Ooboshi H and Yoshimura A: Neuroimmune mechanisms and therapies mediating post-ischaemic brain injury and repair. Nat Rev Neurosci 24: 299-312, 2023.
14. She R, Liu D, Liao J, Wang G, Ge J and Mei Z: Mitochondrial dysfunctions induce PANoptosis and ferroptosis in cerebral ischemia/reperfusion injury: From pathology to therapeutic potential. Front Cell Neurosci 17: 1191629, 2023.
15. Zhang S, Zis O, Ly PTT, Wu Y, Zhang S, Zhang M, Cai F, Bucala R, Shyu WC and Song W: Down-regulation of MIF by NFκB under hypoxia accelerated neuronal loss during stroke. FASEB J 28: 4394-4407, 2014.
16. Kim JA, Kim YY, Lee SH, Jung C, Kim MH and Kim DY: Neuroprotective effect of macrophage migration inhibitory factor (MIF) in a mouse model of ischemic stroke. Int J Mol Sci 23: 6975, 2022.
17. Leng L, Metz CN, Fang Y, Xu J, Donnelly S, Baugh J, Delohery T, Chen Y, Mitchell RA and Bucala R: MIF signal transduction initiated by binding to CD74. J Exp Med 197: 1467-1476, 2003.
18. Yang L, Kong Y, Ren H, Li M, Wei CJ, Shi E, Jin WN, Hao J, Vandenbark AA and Offner H: Upregulation of CD74 and its potential association with disease severity in subjects with ischemic stroke. Neurochem Int 107: 148-155, 2017.
19. Liu YC, Tsai YH, Tang SC, Liou HC, Kang KH, Liou HH, Jeng JS and Fu WM: Cytokine MIF enhances blood-brain barrier permeability: Impact for therapy in ischemic stroke. Sci Rep 8: 743, 2018.
20. Chen HR, Chuang YC, Chao CH and Yeh TM: Macrophage migration inhibitory factor induces vascular leakage via autophagy. Biol Open 4: 244-252, 2015.
21. Simões Da Gama C and Morin-Brureau M: Study of BBB dysregulation in neuropathogenicity using integrative human model of blood-brain barrier. Front Cell Neurosci 16: 863836, 2022.
22. Zis O, Zhang S, Dorovini-Zis K, Wang L and Song W: Hypoxia signaling regulates macrophage migration inhibitory factor (MIF) expression in stroke. Mol Neurobiol 51: 155-167, 2015.
23. Chang MC, Park CR, Rhie SH, Shim WH and Kim DY: Early treadmill exercise increases macrophage migration inhibitory factor expression after cerebral ischemia/reperfusion. Neural Regen Res 14: 1230-1236, 2019.
24. Chen Y, Mao L, Zhou Q, Bai D and Kong Y: Role of BDNF-TrkB signaling in the improvement of motor function and neuroplasticity after ischemic stroke in rats by transcranial direct current stimulation. Brain Res Bull 220: 111164, 2025.

25. Li Y, Li F, Qin D, Chen H, Wang J, Wang J, Song S, Wang C, Wang Y, Liu S, *et al*: The role of brain derived neurotrophic factor in central nervous system. Front Aging Neurosci 14: 986443, 2022.
26. Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG and Murphy RA: Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. J Biol Chem 276: 12660-12666, 2001.
27. Palachai N, Supawat A, Kongsui R, Klimaschewski L and Jittiwat J: Galangin's neuroprotective role: Targeting oxidative stress, inflammation, and apoptosis in ischemic stroke in a rat model of permanent middle cerebral artery occlusion. Int J Mol Sci 26: 1847, 2025.
28. Radak D, Katsiki N, Resanovic I, Jovanovic A, Sudar-Milovanovic E, Zafirovic S, Mousad SA and Isenovic ER: Apoptosis and acute brain ischemia in ischemic stroke. Curr Vasc Pharmacol 15: 115-122, 2017.
29. Ji W, Ren Y, Wei X, Ding X, Dong Y and Yuan B: Ischemic stroke protected by ISO-1 inhibition of apoptosis via mitochondrial pathway. Sci Rep 13: 2788, 2023.
30. Botts SR, Fish JE and Howe KL: Dysfunctional vascular endothelium as a driver of atherosclerosis: Emerging insights into pathogenesis and treatment. Front Pharmacol 12: 787541, 2021.
31. Gui Y, Zheng H and Cao RY: Foam cells in atherosclerosis: Novel insights into its origins, consequences, and molecular mechanisms. Front Cardiovasc Med 9: 845942, 2022.
32. Rudijanto A: The role of vascular smooth muscle cells on the pathogenesis of atherosclerosis. Acta Med Indones 39: 86-93, 2007.
33. Mimura J and Itoh K: Role of Nrf2 in the pathogenesis of atherosclerosis. Free Radic Biol Med 88: 221-232, 2015.
34. Burger-Kentischer A, Goebel H, Seiler R, Fraedrich G, Schaefer HE, Dimmeler S, Kleemann R, Bernhagen J and Ihling C: Expression of macrophage migration inhibitory factor in different stages of human atherosclerosis. Circulation 105: 1561-1566, 2002.
35. Bernhagen J, Krohn R, Lue H, Gregory JL, Zernecke A, Koenen RR, Dewor M, Georgiev I, Schober A, Leng L, *et al*: MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. Nat Med 13: 587-596, 2007.
36. Shi X, Leng L, Wang T, Wang W, Du X, Li J, McDonald C, Chen Z, Murphy JW, Lolis E, *et al*: CD44 is the signaling component of the macrophage migration inhibitory factor-CD74 receptor complex. Immunity 25: 595-606, 2006.
37. Krammer C, Yang B, Reichl S, Besson-Girard S, Ji H, Bolini V, Schulte C, Noels H, Schlepckow K, Jocher G, *et al*: Pathways linking aging and atheroprotection in Mif-deficient atherosclerotic mice. FASEB J 37: e22752, 2023.
38. Amin MA, Haas CS, Zhu K, Mansfield PJ, Kim MJ, Lackowski NP and Koch AE: Migration inhibitory factor up-regulates vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 via Src, PI3 kinase, and NFkappaB. Blood 107: 2252-2261, 2006.
39. Ma J, Luo J, Sun Y and Zhao Z: Cytokines associated with immune response in atherosclerosis. Am J Transl Res 14: 6424-6444, 2022.
40. Onodera S, Kaneda K, Mizue Y, Koyama Y, Fujinaga M and Nishihira J: Macrophage migration inhibitory factor up-regulates expression of matrix metalloproteinases in synovial fibroblasts of rheumatoid arthritis. J Biol Chem 275: 444-450, 2000.
41. Wirtz TH, Tillmann S, Strüßmann T, Kraemer S, Heemskerk JW, Grottke O, Gawaz M, von Hundelshausen P and Bernhagen J: Platelet-derived MIF: A novel platelet chemokine with distinct recruitment properties. Atherosclerosis 239: 1-10, 2015.
42. Burger-Kentischer A, Göbel H, Kleemann R, Zernecke A, Bucala R, Leng L, Finkelmeier D, Geiger G, Schaefer HE, Schober A, *et al*: Reduction of the aortic inflammatory response in spontaneous atherosclerosis by blockade of macrophage migration inhibitory factor (MIF). Atherosclerosis 184: 28-38, 2006.
43. Schober A, Bernhagen J, Thiele M, Zeiffer U, Knarren S, Roller M, Bucala R and Weber C: Stabilization of atherosclerotic plaques by blockade of macrophage migration inhibitory factor after vascular injury in apolipoprotein E-deficient mice. Circulation 109: 380-385, 2004.
44. Adiyeke E, Ren Y, Fogel S, Rashidi P, Segal M, Shenkman EA, Bihorac A and Ozrazgat-Baslanti T: Epidemiology, trajectories and outcomes of acute kidney injury among hospitalized patients: A large retrospective multicenter cohort study. J Nephrol 38: 1673-1682, 2025.
45. Tziastoudi M, Cholevas C, Stefanidis I and Theoharides TC: Immune-related gene polymorphisms and pharmacogenetic studies in nephrology. Clin Ther 43: 2148-2153, 2021.
46. Du Y, Feng C, Zhou L, Wang T, Ma H and Liu H: Biphasic protective effects of macrophage migration inhibitory factor in ischemia/reperfusion-induced acute kidney injury. Commun Biol 8: 1112, 2025.
47. Li T, Zhang J, Long M, Jiang X, Yang C, Wang F, Su L and Peng Z: Macrophage migration inhibitory factor provides a predictive performance of septic acute kidney injury. Shock 57: 666-671, 2022.
48. Du Y, Hao H, Ma H and Liu H: Macrophage migration inhibitory factor in acute kidneyinjury. Front Physiol 13: 945827, 2022.
49. Muruve DA: Inflammasomes and acute kidney injury. J Am Soc Nephrol 35: 985-987, 2024.
50. Stoppe C, Averdunk L, Goetzenich A, Soppert J, Marlier A, Kraemer S, Vieten J, Coburn M, Kowark A, Kim BS, *et al*: The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery. Sci Transl Med 10: eaan4886, 2018.
51. Djudjaj S, Martin IV, Buhl EM, Nothofer NJ, Leng L, Piecychna M, Floege J, Bernhagen J, Bucala R and Boor P: Macrophage migration inhibitory factor limits renal inflammation and fibrosis by counteracting tubular cell cycle arrest. J Am Soc Nephrol 28: 3590-3604, 2017.
52. Guarneri M, Scola L, Giarratana RM, Bova M, Carollo C, Vaccarino L, Calandra L, Lio D, Balistreri CR and Cottone S: MIF rs755622 and IL6 rs1800795 are implied in genetic susceptibility to end-stage renal disease (ESRD). Genes (Basel) 13: 226, 2022.
53. Liu Y, Liu Y, Wang Q, Song Y, Chen S, Cheng B, Zhang Y, Cui Z, Wu Z and Zhu C: MIF inhibitor ISO-1 alleviates severe acute pancreatitis-associated acute kidney injury by suppressing the NLRP3 inflammasome signaling pathway. Int Immunopharmacol 96: 107555, 2021.
54. Filip AM, Klug J, Cayli S, Fröhlich S, Henke T, Lacher P, Eickhoff R, Bulau P, Linder M, Carlsson-Skwirut C, *et al*: Ribosomal protein S19 interacts with macrophage migration inhibitory factor and attenuates its pro-inflammatory function. J Biol Chem 284: 7977-7985, 2009.
55. Sun T, Hu Y, He W, Shang Y, Yang X, Gong L, Zhang X, Gong P and Yang G: SRT2183 impairs ovarian cancer by facilitating autophagy. Aging (Albany NY) 12: 24208-24218, 2020.
56. Averdunk L, Bernhagen J, Fehnle K, Surowy H, Lüdecke HJ, Mucha S, Meybohm P, Wieczorek D, Leng L, Marx G, *et al*: The macrophage migration inhibitory factor (MIF) promoter polymorphisms (rs3063368, rs755622) predict acute kidney injury and death after cardiac surgery. J Clin Med 9: 2936, 2020.
57. Kontos C, El Bounkari O, Krammer C, Sinitski D, Hille K, Zan C, Yan G, Wang S, Gao Y, Brandhofer M, *et al*: Designed CXCR4 mimic acts as a soluble chemokine receptor that blocks atherogenic inflammation by agonist-specific targeting. Nat Commun 11: 5981, 2020.
58. Pekayvaz K, Gold C, Hoseinpour P, Engel A, Martinez-Navarro A, Eivers L, Coletti R, Joppich M, Dionísio F, Kaiser R, *et al*: Mural cell-derived chemokines provide a protective niche to safeguard vascular macrophages and limit chronic inflammation. Immunity 56: 2325-2341.e15, 2023.
59. Li J, Tang Y, Tang PMK, Lv J, Huang XR, Carlsson-Skwirut C, Da Costa L, Aspesi A, Fröhlich S, Szczęśniak P, *et al*: RETRACTED: Blocking macrophage migration inhibitory factor protects against cisplatin-induced acute kidney injury in mice. Mol Ther 26: 2523-2532, 2018.
60. Li T, Sun H, Li Y, Su L, Jiang J, Liu Y, Jiang N, Huang R, Zhang J, Peng Z *et al*: Downregulation of macrophage migration inhibitory factor attenuates NLRP3 inflammasome mediated pyroptosis in sepsis-induced AKI. Cell Death Discov 8: 61, 2022.
61. Li T, Qu J, Hu C, Pang J, Qian Y, Li Y and Peng Z: Macrophage migration inhibitory factor (MIF) suppresses mitophagy through disturbing the protein interaction of PINK1-Parkin in sepsis-associated acute kidney injury. Cell Death Dis 15: 473, 2024.
62. Hu JX, Ma WJ, He LY, Zhang CH, Zhang C, Wang Y, Chen CN, Shen DY, Gao HM, Guo RR, *et al*: Macrophage migration inhibitory factor (MIF) acetylation protects neurons from ischemic injury. Cell Death Dis 13: 466, 2022.
63. Chen Z, Sakuma M, Zago AC, Zhang X, Shi C, Leng L, Mizue Y, Bucala R and Simon D: Evidence for a role of macrophage migration inhibitory factor in vascular disease. Arterioscler Thromb Vasc Biol 24: 709-714, 2004.

64. Walter HL, van der Maten G, Antunes AR, Wieloch T and Ruscher K: Treatment with AMD3100 attenuates the microglial response and improves outcome after experimental stroke. J Neuroinflammation 12: 24, 2015.
65. Rohlfing AK, Kolb K, Sigle M, Ziegler M, Bild A, Münzer P, Sudmann J, Dicenta V, Harm T, Manke MC, *et al*: ACKR3 regulates platelet activation and ischemia-reperfusion tissue injury. Nat Commun 13: 1823, 2022.
66. Samokhin AO, Lythgo PA, Gauthier JY, Percival MD and Brömme D: Pharmacological inhibition of cathepsin S decreases atherosclerotic lesions in Apoe-/- mice. J Cardiovasc Pharmacol 56: 98-105, 2010.
67. Martín-Ventura JL, Madrigal-Matute J, Muñoz-Garcia B, Blanco-Colio LM, Van Oostrom M, Zalba G, Fortuño A, Gomez-Guerrero C, Ortega L, Ortiz A, *et al*: Increased CD74 expression in human atherosclerotic plaques: Contribution to inflammatory responses in vascular cells. Cardiovasc Res 83: 586-594, 2009.
68. Gencer S, Döring Y, Jansen Y, Bayasgalan S, Yan Y, Bianchini M, Cimen I, Müller M, Peters LJF, Megens RTA, *et al*: Endothelial ACKR3 drives atherosclerosis by promoting immune cell adhesion to vascular endothelium. Basic Res Cardiol 117: 30, 2022.
69. Liu P, Li X, Lv W and Xu Z: Inhibition of CXCL1-CXCR2 axis ameliorates cisplatin-induced acute kidney injury by mediating inflammatory response. Biomed Pharmacother 122: 109693, 2020.
70. Zuk A, Gershenovich M, Ivanova Y, MacFarland RT, Fricker SP and Ledbetter S: CXCR4 antagonism as a therapeutic approach to prevent acute kidney injury. Am J Physiol Renal Physiol 307: F783-F797, 2014.