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REVIEW ARTICLE

TARGETING MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF): SMALL-MOLECULE INHIBITORS AND THERAPEUTIC STRATEGIES FOR IMMUNE DISORDERS AND CANCER

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ABSTRACT

Macrophage Migration Inhibitory Factor (MIF) is a critical cytokine implicated in various human disorders, with significant roles in innate and acquired immunity and inflammatory diseases. Recent investigations have linked MIF to the pathophysiology of cancer. Extensive research has been dedicated to studying its structure and actions, leading to its classification as both an enzyme and a hormone. Its isomerase enzymatic activity is exciting, which has sparked enthusiasm for developing specific small-molecule inhibitors targeting this unique enzymatic function to treat inflammatory illnesses potentially. While there is growing awareness of MIF's importance in inflammation and cancer, the availability of adequate and extensively studied MIF inhibitors for relevant disease models remains limited. Advancing drug discovery necessitates the development of highly potent and selective small-molecule MIF inhibitors, along with rigorous validation in disease models. Our review article comprehensively summarizes recent progress recognizing MIF as a pharmaceutical target for inflammatory conditions and cancer. Furthermore, it highlights promising areas for future research in this domain and outlines recent advancements in identifying and designing small-molecule MIF inhibitors. These efforts aim to facilitate the development of novel therapies that target MIF and have the potential to address various disease conditions associated with its dysregulation.

KEY WORDS: Cancer; Cytokine; Inflammatory diseases; Macrophage migration inhibitory factor (MIF); Small-molecule inhibitors; Therapeutic potential.

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I. INTRODUCTION

In 1966, Bloom and David made a groundbreaking discovery by identifying Macrophage Migration Inhibitory Factor (MIF) as an inflammatory cytokine produced by T-cells.[1,2] Since then, the role of MIF in innate immune responses has been widely acknowledged, and its association with various disease processes has been extensively studied.[3-5] Notably, the multifaceted roles of MIF in inflammation and the development of diseases have attracted considerable attention, prompting the exploration of therapeutic strategies targeting this intriguing molecule.[6]

Macrophage Inflammatory Factor (MIF) is synthesized at sites of inflammation in response to infections and plays a crucial role in attracting and activating macrophages. These immune cells are integral to several immunological processes, including antigen processing and phagocytosis, contributing significantly to the body's defense against external intruders and the avoidance of infections.[3] The innate immune response, orchestrated by macrophages, is pivotal in mounting early defenses against pathogens and maintaining tissue homeostasis.

Given its involvement in various disease processes over time, MIF has emerged as an attractive candidate for therapeutic development. Numerous disorders, such as atherosclerosis, acute respiratory distress syndrome (ARDS), and rheumatoid arthritis, have been linked to the dysregulation of MIF.[7-9] Additionally, the intriguing combination of MIF's cytokine

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activity and its isomerase enzymatic activity has piqued the interest of researchers seeking to unravel its precise functions in biological systems.[10,11]

Despite extensive research on the functional importance of MIF in various disease models, the identification and validation of the functional consequences of small-molecule MIF tautomerase inhibitors are still in the early stages.[12] The design of small-molecule inhibitors targeting MIF holds promise for disrupting both its cytokine and enzymatic functions, offering a specific means to target inflammation and the underlying mechanisms of illness.[13,14] This potential for targeted interventions presents exciting opportunities for therapeutic applications.

The primary objective of this comprehensive research is to provide a detailed analysis of the latest advancements in understanding the therapeutic potential of MIF as a target in the pathogenesis of inflammatory diseases and cancer. The chapter will focus on elucidating the roles of MIF in innate immunity, inflammation, and disease processes. Furthermore, an in-depth analysis will be conducted on the mechanisms by which small-molecule MIF inhibitors operate, as well as their potential applications in therapy.

By exploring the current state of research in this field and identifying future goals, this review artilce aims to contribute valuable insights into the development of MIF-targeted therapeutics and their potential impact on improving patient outcomes in various disease conditions associated with MIF dysregulation.

2. PROTEIN STRUCTURE

The protein structure of Macrophage Migration Inhibitory Factor (MIF) plays a pivotal role in various biological processes. MIF's existence as a homo trimer, consisting of three identical subunits, has been firmly established through X-ray crystallography and Nuclear Magnetic Resonance (NMR) investigations (Figure 1).[15] Previous studies have conclusively demonstrated that MIF's molecular enzymatic activity depends on the carboxy terminus.[16-18] Of particular importance is the terminal proline (Pro-1) located at the carboxy terminus, which serves as a crucial catalytic base, facilitating MIF's isomerase enzymatic activity.[19] The precise positioning of Pro-1 plays a critical role in enabling the tautomerase activity of MIF. Notably, this activity is entirely abolished when introducing an alanine residue between Pro-1 and Met-2 or substituting proline with either serine or glycine.[20-22] Recent research has provided further insights into the significance of the carboxy terminal region, both in MIF's enzymatic activity and its overall three-dimensional structure.[18] These notable discoveries contribute to a deeper understanding of MIF's distinct molecular properties and its diverse biological roles, making it an intriguing and valuable subject for future investigations across various academic disciplines.

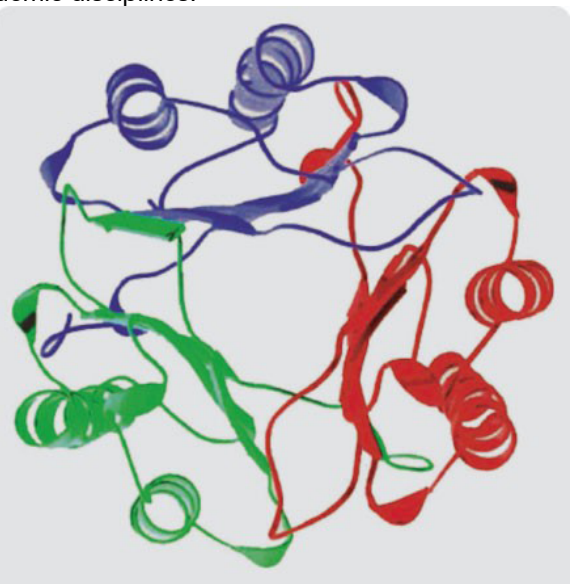

Figure 1: Trimeric structure of MIF protein

Figure 1 illustrates the trimeric structure of the MIF protein, where blue, red, and green colors represent the individual components.[16] For a color illustration, please refer to the online version available at http://www.interscience.wiley.com/.

A. Pathophysiological Significance: In normal physiological conditions, the macrophage migration inhibitory factor (MIF) concentration ranges from 2 ng/ml to 6 ng/ml, exhibiting a diurnal pattern associated with plasma cortisol levels.[23] However, the pathogenic consequences of MIF have been recognized, particularly its clinical feature of counteracting the inhibitory impact of glucocorticoids on cytokine synthesis when released into the circulatory system due to reduced glucocorticoid levels. This negates the beneficial effects of glucocorticoids in alleviating potentially fatal inflammation caused by endotoxins.[24]

Various acute inflammatory conditions, such as glomerulonephritis, acute lung injury, sepsis, and acute pancreatitis, significantly influence the activity of MIF. Studies have associated the presence of varying amounts of MIF in the human body with the severity and progression of numerous clinical disorders.[25] MIF's enzymatic activities, including well-documented tautomerase activity, have been studied, particularly in tautomerization processes of phenylpyruvate, p-hydroxyphenylpyruvate, and D-dopachrome.[26]

Furthermore, MIF regulates cell cycle advancement through its interaction with the constitutive photomorphogenic-9 (CSN5) signalosome, also known as the fifth component of the c-Jun activation binding protein-1 (JAB1) dependent pathways. This interaction leads to the degradation of the cyclin-dependent kinase inhibitor p27Kip1, promoting cell cycle

progression.[27]

Recent research has emphasized the importance of MIF's carboxy-terminal region in maintaining its overall three-dimensional structure and enzymatic activity. These findings provide significant insights into MIF's unique molecular characteristics and diverse biological functions, making it a compelling subject for future exploration in various scientific fields.

B. Enzymatic Activity of Macrophage Migration Inhibitory Factor (MIF): Macrophage Migration Inhibitory Factor (MIF) has been extensively studied for its enzymatic activity. Its tautomerase activity, akin to bacterial enzymes CHMI and DOPD, has been identified, supporting its mode of action.[14] Further research has revealed its interaction with phenylpyruvate and p-hydroxyphenylpyruvate.[26] Additionally, MIF acts as an enzyme involved in thiol-protein oxidation-reduction reactions, converting harmful quinone byproducts of neurotransmitter catecholamines into indole-dihydroxy derivatives, potentially influencing neuromelanin production.[28, 29]

Therapeutic implications of MIF's enzymatic activity have been explored, focusing on developing specific inhibitors targeting MIF tautomerase activity.[18] Notably, ISO-1, a known MIF inhibitor, effectively reduced cytokine activity and improved survival rates in a mouse sepsis model.[30] Recent research highlights the inhibitor 4-iodo-6-phenylpryimidine (4-ipp) as a promising "suicide substrate" that irreversibly inhibits MIF, particularly in lung cancer cells, showing greater efficiency than ISO-1.[31]

The link between myeloid-derived suppressor cells (MDSCs), chronic inflammation, and cancer development has garnered significant attention. Various epidemiological studies have associated chronic inflammatory conditions with increased susceptibility to cancer.[32] Recent literature reviews underscore the potential significance of MIF as a critical link between excessive inflammation and cancer progression.[14]

The potential therapeutic applications of MIF's C-terminal region warrant further investigation. A comprehensive understanding of the clinical consequences of MIF's enzymatic activity is essential, and the development of targeted inhibitors holds promise for novel treatment approaches. Continued research in this area will advance our knowledge of MIF's enzymatic functions and its potential as a therapeutic target.

C. MIF, Inflammation, and Cancer: Multiple malignancies, including breast, colon, liver, lung, neuroblastoma, and prostate, have been associated with an increased expression of Macrophage Migration Inhibitory Factor (MIF).[33-39] In the context of gastric epithelial cells, CagA, a protein synthesized by Helicobacter pylori, has been studied to understand its effects on MIF production and CD-74 expression, showing similar outcomes to those of H. pylori.[40] This interaction between CagA and MIF has been observed to promote cellular proliferation.[41]

The role of MIF in tumor formation is believed to be linked to its inhibition of p53, a tumor suppressor gene responsible for impeding cancer progression and tumor development.[42] In breast cancer, elevated MIF levels have been associated with increased angiogenic factors such as IL-8 and VEGF, leading to a poorer clinical prognosis.[43] Additionally, MIF has been found to impair the ability of natural killer (NK) cells to eradicate ovarian cancer tumor cells by reducing NK group 2D expression in both laboratory and clinical settings.[44] Animal studies involving MIF-deficient models have demonstrated significantly slower cancer progression. At the same time, decreased MIF levels have been associated with a reduced inflammatory response in the epidermis after exposure to UVB radiation.[45]

These findings underscore the potential significance of MIF in cancer initiation and progression, particularly in the context of persistent inflammation. However, further research is imperative to gain a comprehensive understanding of MIF's precise mechanisms and therapeutic implications in cancer.

3. MIF TARGETED TREATMENT STRATEGIES

Figure 2 illustrates several techniques for antagonizing MIF in the context of targeted treatment strategies for myocardial infarction (MIF).These therapeutic approaches offer intriguing possibilities to modulate MIF activity and functionality, thereby presenting promising avenues for the development of revolutionary treatments that target cancer, malignant disorders, and other diseases influenced by MIF.

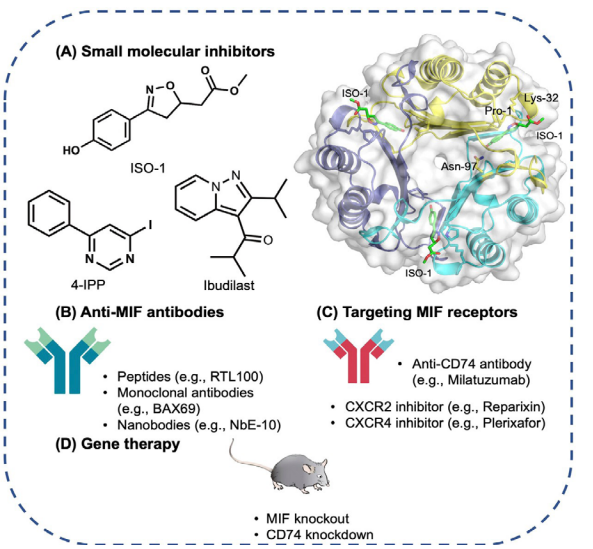

Figure 2: Therapeutic techniques targeting macrophage migration inhibitory factor (MIF)

Figure 2 showcases various therapeutic techniques that specifically target Macrophage Migration Inhibitory Factor (MIF). Notably, the molecules ISO-1,

4-IPP, and Ibudilast have been identified for their ability to bind to the active site of MIF tautomerase. Through interactions with specific residues in MIF, these compounds induce structural modifications that hinder MIF's binding to CD74 and alter the functioning of MIF and its structural homolog DDT. Monoclonal antibodies have also been designed to target MIF molecules and inhibit their functionality effectively. Additionally, small-molecule inhibitors, including CD74, CXCR2, CXCR4, and CXCR7, have been developed to specifically target MIF receptors and interact with them. Another therapeutic avenue involves gene therapy, employing techniques to modify genes associated with MIF, such as Mif, DDT, or CD74, through gene deletion or knockdown processes.

A. Small Molecular Inhibitors: A class of chemical substances known as small molecular inhibitors exhibit selective binding to specific target molecules, disrupting their normal functions. These inhibitors are characterized by relatively low molecular weights, setting them apart from other drugs. Previous research has demonstrated the efficacy of small molecule inhibitors targeting Macrophage Migration Inhibitory Factor (MIF) in mitigating inflammation in various animal models, including severe sepsis, rheumatoid arthritis, allergic airway inflammation, colitis, and glomerulonephritis.[46-50] Expert assessments of advancements in MIF inhibitors have been extensively covered in the literature.[51-53] Moreover, the effectiveness of small inhibitory compounds specifically targeting MIF has been confirmed in diverse experimental cancer models, such as lung cancer, bladder cancer, adenoid cystic carcinoma, melanoma, and colon cancer.[54-57]

Recent discoveries have highlighted the focus on rational structure-based design in advancing small-molecule MIF inhibitors. These inhibitors selectively block MIF's tautomerase activity and its binding to CD74. Several significant investigations have explored this approach.[51,53,58-60] However, progress in small molecule MIF inhibitors has faced challenges due to the absence of a reliable and widely-used in vitro test for evaluating MIF's biological functioning. Future research is recommended to prioritize the creation of a clinically helpful MIF bioassay with traits like high throughput and reproducibility. This bioassay holds promise for various applications, including second-pass screening, glucocorticoid override, cellular proliferation assessment, and cytokine release detection.

As stated by Bloom et al. (2016 b)[61], the main objective is to facilitate the development of efficient small molecule inhibitors that specifically target MIF. While research on the effects of ISO-1 and 4-IPP concerning acute pancreatitis (AP) and pancreatic ductal adenocarcinoma (PDAC) has been limited to experimental animal models, further investigation is needed to evaluate the efficacy of small molecule MIF inhibitors in both controlled laboratory experiments and live organism environments. These efforts play a pivotal role in augmenting the current body of data and advancing the potential therapeutic use of these inhibitors.

B. Anti-MIF Antibodies: Within the realm of academic investigation, two separate studies conducted by Sakai et al. (2003)[62] and Matsuda et al. (2006)[63] have demonstrated the efficacy of anti-MIF antibodies in animal models of acute pancreatitis (AP). Sakai et al. (2003)[62] aimed to examine the effectiveness of anti-MIF antibodies in an animal model of AP induced by cerulein and lipopolysaccharide (CER/LPS), while Matsuda et al. (2006)[63] evaluated their use in a different AP model induced by a choline-deficient, ethionine-supplemented (CDE) diet. The collective findings of these investigations indicate promising therapeutic potential for targeting MIF in managing acute pancreatitis (AP).

Additionally, Sparkes et al. (2018)[64] conducted a study showcasing the efficacy of nanobodies, specifically NbE5 and NbE10, in reducing death rates in an animal model of septic shock. This research has garnered considerable attention due to its implications for the potential use of nanobodies in various scenarios involving inflammatory injury to vital organs, such as severe acute pancreatitis.

Researchers at Baxter have successfully developed a range of monoclonal antibodies that exhibit high specificity in targeting macrophage migration inhibitory factor (MIF). Hussain et al. (2013)[65] reported on the effectiveness of these antibodies in suppressing MIF activity in human PC3 prostate cancer cell lines and in vivo xenograft models. In vitro, studies have revealed that BaxG03, BaxB01, and BaxM159 possess inhibitory properties on cellular proliferation and viability by interacting with the ERK1/2 and AKT signaling cascades. Moreover, these antibodies have demonstrated the ability to inhibit migratory and invasive pathways activated by MIF. In vivo, investigations have shown that treatment with anti-MIF antibodies results in reduced tumor formation, with the extent of reduction dependent on the administered dose.

The efficacy of Imalumab (Bax69) was evaluated in individuals diagnosed with solid tumors and metastatic colorectal adenocarcinoma in a recent phase 1 clinical study conducted by Mahalingam et al. (2020).[66] The study revealed that imalumab exhibited a maximum tolerated dosage of 37.5 mg/kg when administered once every two weeks. A dosage of 10 mg/kg administered weekly demonstrated biological activity. Further research is needed to elucidate the precise role of anti-MIF antibodies in treating pancreatic cancer.

While antibodies have shown effectiveness, it is crucial to consider their finite duration of activity,

significant production costs, and potential to induce an immune response. These factors may impose limitations on their widespread utilization in clinical settings. Therefore, further research is necessary to enhance the clinical effectiveness of alternative therapy approaches targeting MIF modulation.

C. Targeting MIF Receptors: The primary objective of this chapter is to investigate the regulation of MIF receptors, with a particular focus on CD74, which plays a crucial role in controlling various biological processes following MIF signaling. Therapies targeting CD74 hold promise in inhibiting MIF signaling effectively.

Milatuzumab is a humanized monoclonal antibody that explicitly targets CD74. Preclinical studies by Stein et al. (2004, 2009)[67, 68] involving xenograft mice models with multiple myeloma demonstrated that milatuzumab significantly extended their lifespan. The experimental medicine has now advanced to the first stage of human studies, where it has been tested in individuals with multiple myeloma[69] and systemic lupus erythematosus[70] with no significant side effects observed.

Researchers are also exploring CD74 inhibitors and other drugs within the MIF pathway, such as Reparixin (a CXCL2 inhibitor) and Plerixafor (a CXCL4 inhibitor).[71,72] The MIF/CD74 pathway activates pro-survival and regenerative mechanisms that protect the organism during damage[73], making it crucial for wound healing. However, careful consideration is required when contemplating a complete CD74 blockade, as it may lead to unintended adverse effects. Proper measurement and alignment of treatment methods are essential to avoid any unintended side effects in clinical applications.

4. MIF-RELATED GENE THERAPY

The observation that MIF knockout mice live longer than wild-type mice without any apparent health issues provides a favorable foundation for exploring gene therapy directly targeting MIF-associated activities.[74] In the context of treating acute pancreatitis (AP) and pancreatic ductal adenocarcinoma (PDAC), gene therapy targeting MIF-related genes, such as Mif, DDT, or CD74, has shown promise.[63,75]

Furthermore, Kindt et al. (2013)[76] demonstrated that reducing macrophage migration inhibitory factor (MIF) expression increased the susceptibility of a xenograft model of head and neck squamous cell carcinoma to cisplatin and 5-fluorouracil therapy. In contrast, Funamizu et al. (2013)[77] found that overexpression of MIF in pancreatic cancer cells reduced the efficiency of gemcitabine therapy. These findings collectively suggest that inhibiting MIF could potentially enhance the efficacy of chemotherapeutic drugs in cancer treatment.

Ongoing research holds promise for the future clinical evaluation of MIF-suppressing treatment strategies. Gene therapy targeting genes associated with MIF (Macrophage Migration Inhibitory Factor) presents a potential avenue for developing effective therapies for various disorders.

5. PROSPECTS FOR INHIBITOR DEVELOPMENT

The development of MIF inhibitors offers a wide range of structural options to target MIF tautomerase activity efficiently. These include direct competition, allosteric regulation, and covalent binding, valuable resources for creating novel structural patterns to block MIF's cytokine effects effectively. In order to determine the binding capability of these inhibitors to cellular receptors like CD74, CXCR2, CXCR4, and CXCR7, various experiments are necessary. Studying these inhibitors in disease models will provide valuable insights into their potential therapeutic applications.

Overcoming several challenges is crucial in the process of inhibitor creation. Cisneros et al. (2016)[78] found that the quoted IC50 values of MIF tautomerase inhibitors may not consistently reflect their true inhibitory strength. Furthermore, some inhibitors were less effective than in previous studies. Considering the time-dependent properties of covalent or slow-tight-binding inhibitors, which are often overlooked, assessing potential reversibility using enzyme dilution studies is necessary. The sigmoidal nature of enzyme kinetics associated with MIF's tautomerase activity toward its substrate, p-hydroxyphenylpyruvate (4-HPP), makes it challenging to calculate the Michaelis-Menten constant (Km) and inhibition equilibrium constant (Ki) based solely on IC50 values. Thus, it is recommended to broaden its scope by including enzyme dilution experiments, kinetic studies, or direct binding assays in MIF binding research. Addressing these issues will contribute to developing more reliable and effective MIF inhibitors.

6. CONCLUSION

The intricate association between MIF and various health conditions, encompassing cancer, chronic inflammatory disorders, and tissue repair, suggests its potential application in regenerative medicine. Moreover, MIF's crucial role in regulating immunological responses, particularly T-cell activation and polarization, underscores its significance in studying immune-related illnesses and developing immunotherapeutic approaches.

MIF serves as a promising biomarker for disease identification and assessment of severity, enabling timely interventions and personalized treatment strategies. Research on MIF genetic polymorphisms has also provided insights into an individual's susceptibility to inflammatory disorders and cancer, paving the way for precision treatment methods. To enhance

the potential effectiveness of MIF inhibitors while minimizing off-target effects, novel delivery systems such as nanoparticle-based drug carriers can be developed. Additionally, advancements in gene editing technologies like CRISPR-Cas9 hold the promise of precise control over MIF expression, offering new therapeutic opportunities. As our understanding of MIF's intricate involvement in health and disease continues to expand, the subject has sparked significant interest for further research across various scientific domains. Ongoing MIF research and the development of tailored medications have the potential to revolutionize healthcare and improve patient outcomes in diverse conditions

REFERENCES

1. Bloom BR, Bennett B. Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science. 1996;153:3.
2. David J. Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc Natl Acad Sci U S A. 1966;56:6. https://doi.org/10.1073/pnas.56.1.72.
3. Nishihira J, Koyama Y, Mizue Y. Identification of macrophage migration inhibitory factor (MIF) in human vascular endothelial cells and its induction by lipopolysaccharide. Cytokine. 1998;10:199-205. https://doi.org/10.1006/cyto.1997.0276.
4. Rossi AG, Haslett C, Hirani N, Greening AP, Rahman I, Metz CN, et al. Human circulating eosinophils secrete macrophage migration inhibitory factor (MIF). Potential role in asthma. J Clin Invest. 1998;101:2869-2874. https://doi.org/10.1172/JCI1524.
5. Imamura K, Nishihira J, Suzuki M, Yasuda K, Sasaki S, Kusunoki Y, et al. Identification and immunohistochemical localization of macrophage migration inhibitory factor in human kidney. Biochem Mol Biol Int. 1996;40:1233-1242. https://doi.org/10.1080/15216549600201883.
6. Shimizu T. Role of macrophage migration inhibitory factor (MIF) in the skin. J Dermatol Sci. 2005;37:65-73. https://doi.org/10.1016/j.jdermsci.2004.08.007.
7. Bacher M, Metz CN, Calandra T, Mayer K, Chesney J, Lohoff M, et al. An essential regulatory role for macrophage migration inhibitory factor in T-cell activation. Proc Natl Acad Sci U S A. 1996;93:7849-7854. https://doi.org/10.1073/pnas.93.15.7849.
8. Calandra T, Bernhagen J, Mitchell RA, Bucala R. The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. J Exp Med. 1994;179:1895-1902. https://doi.org/10.1084/jem.179.6.1895.
9. Daryadel A, Grifone RF, Simon HU, Yousefi S. Apoptotic neutrophils release macrophage migration inhibitory factor upon stimulation with tumor necrosis factor-alpha. J Biol Chem. 2006;281:27653-27661. https://doi.org/10.1074/jbc.M604051200.
10. Pan JH, Sukhova GK, Yang JT, Wang B, Xie T, Fu H, et al. Macrophage migration inhibitory factor deficiency impairs atherosclerosis in low-density lipoprotein receptor-deficient mice. Circulation. 2004;109:3149-3153. https://doi.org/10.1161/01.CIR.0000134704.84454.D2.
11. Donnelly SC, Haslett C, Reid PT, Grant IS, Wallace WA, Metz CN, et al. Regulatory role for macrophage migration inhibitory factor in acute respiratory distress syndrome. Nat Med. 1997;3:320-323. https://doi.org/10.1038/nm0397-320.
12. Morand EF, Leech M, Weedon H, Metz CN, Bucala R, Smith MD. Macrophage migration inhibitory factor in rheumatoid arthritis: clinical correlations. Rheumatology (Oxford). 2002;41:558-562. https://doi.org/10.1093/rheumatology/41.5.558.
13. Bucala R, Donnelly SC. Macrophage migration inhibitory factor: a probable link between inflammation and cancer. Immunity. 2007;26:281-285. https://doi.org/10.1016/j.immuni.2007.03.005.
14. Rosengren E, Bucala R, Aman P, Jacobsson L, Odh G, Metz CN, Rorsman H. The immunoregulatory mediator macrophage migration inhibitory factor (MIF) catalyzes a tautomerization reaction. Mol Med. 1996;2:143-149. https://doi.org/10.1007/BF03402210.
15. Sun HW, Swope M, Cinquina C, Bedarkar S, Bernhagen J, Bucala R, Lolis E. The subunit structure of human macrophage migration inhibitory factor: evidence for a trimer. Protein Eng. 1996;9:631-635. https://doi.org/10.1093/protein/9.8.631.
16. Baugh JA, Bucala R. Macrophage migration inhibitory factor. Crit Care Med. 2002;30(Suppl 1):S27-S35. https://doi.org/10.1097/00003246-200201001-00004.
17. Mischke R, Gessner A, Kapurniotu A, Juttner S, Kleemann R, Brunner H, Bernhagen J. Structure activity studies of the cytokine macrophage migration inhibitory factor (MIF) reveal a critical role for its carboxy terminus. FEBS Lett. 1997;414:226-232. https://doi.org/10.1016/S0014-5793(97)01039-9.
18. El-Turk F, Cascella M, Ouertatani-Sakouhi H, Narayanan RL, Leng L, Bucala R, et al. The conformational flexibility of the carboxy terminal residues 105-114 is a key modulator of the catalytic activity and stability of macrophage migration inhibitory factor. Biochemistry. 2008;47:10740-10756. https://doi.org/10.1021/bi800603x.
19. Stamps SL, Fitzgerald MC, Whitman CP. Characterization of the role of the amino-terminal proline in the enzymatic activity catalyzed by macrophage migration inhibitory factor. Biochemistry. 1998;37:10195-10202. https://doi.org/10.1021/bi9806955.
20. Swope M, Sun HW, Blake PR, Lolis E. Direct link between cytokine activity and a catalytic site for macrophage migration inhibitory factor. EMBO J. 1998;17:3534-3541. https://doi.org/10.1093/emboj/17.13.3534.
21. Bendrat K, Al-Abed Y, Callaway DJ, Peng T, Calandra T, Metz CN, Bucala R. Biochemical and mutational investigations of the enzymatic activity of macrophage migration inhibitory factor. Biochemistry. 1997;36:15356-15362. https://doi.

org/10.1021/bi971153a.

22. Lubetsky JB, Swope M, Dealwis C, Blake P, Lolis E. Pro-1 of macrophage migration inhibitory factor functions as a catalytic base in the phenylpyruvate tautomerase activity. Biochemistry. 1999;38:7346-7354. https://doi.org/10.1021/bi990306m.
23. Petrovsky N, Socha L, Silva D, Grossman AB, Metz C, Bucala R. Macrophage migration inhibitory factor exhibits a pronounced circadian rhythm relevant to its role as a glucocorticoid counter-regulator. Immunol Cell Biol. 2003;81:137-143. https://doi.org/10.1046/j.0818-9641.2002.01148.x.
24. Bloom J, Metz C, Nalawade S, Casabar J, Cheng KF, He M, et al. Identification of iguratimod as an inhibitor of macrophage migration inhibitory factor (MIF) with steroid-sparing potential. J Biol Chem. 2016;291:26502-26514. https://doi.org/10.1074/jbc.M116.743328.
25. Harris J, Vanpatten S, Deen NS, Al-Abed Y, Morand EF. Rediscovering MIF: new tricks for an old cytokine. Trends Immunol. 2019;40:447-462. https://doi.org/10.1016/j.it.2019.03.002.
26. Rosengren E, Åman P, Thelin S, Hansson C, Ahlfors S, Björk P, et al. The macrophage migration inhibitory factor MIF is a phenyl pyruvate tautomerase. FEBS Lett. 1997;417:85-88. https://doi.org/10.1016/S0014-5793(97)01261-1.
27. Kleemann R, Hausser A, Geiger G, Mischke R, Burger-Kentischer A, Flieger O, et al. Intracellular action of the cytokine MIF to modulate AP-1 activity and the cell cycle through Jab1. Nature. 2000;408:211-216. https://doi.org/10.1038/35041591.
28. Kleemann R, Kapurniotu A, Frank RW, Gessner A, Mischke R, Flieger O, Juttner S, Brunner H, Bernhagen J. Disulfide analysis reveals a role for macrophage migration inhibitory factor (MIF) as thiol-protein oxidoreductase. J Mol Biol. 1998;280:85-102. https://doi.org/10.1006/jmbi.1998.1864.
29. Matsunaga J, Sinha D, Pannell L, Santis C, Solano F, Wistow GJ, Hearing VJ. Enzyme activity of macrophage migration inhibitory factor toward oxidized catecholamines. J Biol Chem. 1999;274:3268-3271. https://doi.org/10.1074/jbc.274.6.3268.
30. Al-Abed Y, Dabideen D, Aljabari B, Valster A, Messmer D, Ochani M, et al. ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis. J Biol Chem. 2005;280:36541-36544. https://doi.org/10.1074/jbc.C500243200.
31. Winner M, Meier J, Zierow S, Rendon BE, Crichlow GV, Riggs R, et al. A novel, macrophage migration inhibitory factor suicide substrate inhibits motility and growth of lung cancer cells. Cancer Res. 2008;68:7253-7257. https://doi.org/10.1158/0008-5472.CAN-07-6227.
32. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell. 2006;124:823-835. https://doi.org/10.1016/j.cell.2006.02.016.
33. Bini L, Magi B, Marzocchi R, Arcuri F, Tripodi S, Cintorino M, et al. Protein expression profiles in human breast ductal carcinoma and histologically normal tissue. Electrophoresis. 1997;18:2832-2841. https://doi.org/10.1002/elps.1150181519.
34. Armstrong ME, Gantier M, Li L, Chung WY, McCann A, Baugh JA, Donnelly SC. Small interfering RNAs induce macrophage migration inhibitory factor production and proliferation in breast cancer cells via a double-stranded RNA-dependent protein kinase-dependent mechanism. J Immunol. 2008;180:7125-7133. https://doi.org/10.4049/jimmunol.180.11.7125.
35. Wilson JM, Coletta PL, Cuthbert RJ, Scott N, MacLennan K, Hawcroft G. Macrophage migration inhibitory factor promotes intestinal tumorigenesis. Gastroenterology. 2005;129:1485-1503. https://doi.org/10.1053/j.gastro.2005.07.061.
36. Akbar SM, Abe M, Murakami H, Tanimoto K, Kumagi T, Yamashita Y, et al. Macrophage migration inhibitory factor in hepatocellular carcinoma and liver cirrhosis; relevance to pathogenesis. Cancer Lett. 2001;171:125-132. https://doi.org/10.1016/S0304-3835(01)00606-1.
37. Kamimura A, Kamachi M, Nishihira J, Ogura S, Isobe H, Dosaka-Akita H, et al. Intracellular distribution of macrophage migration inhibitory factor predicts the prognosis of patients with adenocarcinoma of the lung. Cancer. 2000;89:334-341. https://doi.org/10.1002/1097-0142(20000715)89:2<334::AID-CNCR18>3.0.CO;2-N.
38. Bin Q, Johnson BD, Schauer DW, Casper JT, Orentas RJ. Production of macrophage migration inhibitory factor by human and murine neuroblastoma. Tumour Biol. 2002;23:123-129. https://doi.org/10.1159/000064028.
39. Meyer-Siegler PBK. Enhanced expression of macrophage migration inhibitory factor in prostatic adenocarcinoma metastases. Urology. 1996;48:448-452. https://doi.org/10.1016/S0090-4295(96)00207-5.
40. Xia HH, Lam SK, Chan AO, Lin MC, Kung HF, Ogura K, et al. Macrophage migration inhibitory factor stimulated by Helicobacter pylori increases proliferation of gastric epithelial cells. World J Gastroenterol. 2005;11:1946-1950. https://doi.org/10.3748/wjg.v11.i13.1946.
41. Meyer-Siegler KL, Iczkowski KA, Vera PL. Further evidence for increased macrophage migration inhibitory factor expression in prostate cancer. BMC Cancer. 2005;5:73. https://doi.org/10.1186/1471-2407-5-73.
42. Fingerle-Rowson G, Petrenko O, Metz CN, Forsthuber TG, Mitchell R, Huss R, et al. The p53-dependent effects of macrophage migration inhibitory factor revealed by gene targeting. Proc Natl Acad Sci U S A. 2003;100:9354-9359. https://doi.org/10.1073/pnas.1533295100.
43. Xu X, Wang B, Ye C, Yao C, Lin Y, Huang X, et al. Overexpression of macrophage migration inhibitory factor induces angiogenesis in human breast cancer. Cancer Lett. 2008;261:147-157. https://doi.org/10.1016/j.canlet.2007.11.028.

44. Krockenberger M, Dombrowski Y, Weidler C, Ossadnik M, Honig A, Hausler S, et al. Macrophage migration inhibitory factor contributes to the immune escape of ovarian cancer by down-regulating NKG2D. J Immunol. 2008;180:7338-7348. https://doi.org/10.4049/jimmunol.180.11.7338.

45. Martin J, Duncan FJ, Keiser T, Shin S, Kusewitt DF, Oberyszyn TM, et al. Macrophage migration inhibitory factor (MIF) plays a critical role in pathogenesis of ultraviolet-B (UVB)-induced nonmelanoma skin cancer (NMSC). FASEB J. 2009;23:720-730. https://doi.org/10.1096/fj.08-119628.

46. Calandra T, Echtenacher B, Roy DL, Pugin J, Metz CN, Hültner L, et al. Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nat Med. 2000;6:164-170. https://doi.org/10.1038/72262.

47. Mikulowska A, Metz CN, Bucala R, Holmdahl R. Macrophage migration inhibitory factor is involved in the pathogenesis of collagen type II-induced arthritis in mice. J Immunol. 1997;158:5514-5517. https://doi.org/10.4049/jimmunol.158.11.5514.

48. Amano T, Nishihira J, Miki I. Blockade of macrophage migration inhibitory factor (MIF) prevents the antigen-induced response in a murine model of allergic airway inflammation. Inflamm Res. 2007;56:24-31. https://doi.org/10.1007/s00011-007-5184-9.

49. Ohkawara T, Nishihira J, Takeda H, Hige S, Kato M, Sugiyama T, et al. Amelioration of dextran sulfate sodium-induced colitis by anti-macrophage migration inhibitory factor antibody in mice. Gastroenterology. 2002;123:256-270. https://doi.org/10.1053/gast.2002.34236.

50. Brown FG, Nikolic-Paterson DJ, Hill PA, Isbel NM, Dowling J, Metz CM, et al. Urine macrophage migration inhibitory factor reflects the severity of renal injury in human glomerulonephritis. J Am Soc Nephrol. 2002;13 Suppl 1 . https://doi.org/10.1681/ASN.V13suppl_1s7

51. Xu L, Li Y, Sun H, Zhen X, Qiao C, Tian S, et al. Current developments of macrophage migration inhibitory factor (MIF) inhibitors. Drug Discov Today. 2013;18:592-600. https://doi.org/10.1016/j.drudis.2012.12.013.

52. Kok T, Wasiel AA, Cool RH, Melgert BN, Poelarends GJ, Dekker FJ. Small-molecule inhibitors of macrophage migration inhibitory factor (MIF) as an emerging class of therapeutics for immune disorders. Drug Discov Today. 2018;23:1910-1918. https://doi.org/10.1016/j.drudis.2018.06.017.

53. Trivedi-Parmar V, Jorgensen WL. Advances and insights for small molecule inhibition of macrophage migration inhibitory factor. J Med Chem. 2018;61:8104-8119. https://doi.org/10.1021/acs.jmedchem.8b00589.

54. Mawhinney L, Armstrong ME, O'Reilly C, Bucala R, Leng L, Fingerle-Rowson G, et al. Macrophage migration inhibitory factor (MIF) enzymatic activity and lung cancer. Mol Med. 2015;20:729-735. https://doi.org/10.2119/molmed.2014.00136.

55. Choudhary S, Hegde P, Pruitt JR, Sielecki TM, Choudhary D, Scarpato K, et al. Macrophage migratory inhibitory factor promotes bladder cancer progression via increasing proliferation and angiogenesis. Carcinogenesis. 2013;34:2891-2899. https://doi.org/10.1093/carcin/bgt239.

56. Liu H, Chen G, Zhang W, Zhu JY, Lin ZQ, Gong ZC, et al. Overexpression of macrophage migration inhibitory factor in adenoid cystic carcinoma: correlation with enhanced metastatic potential. J Cancer Res Clin Oncol. 2013;139:287-295. https://doi.org/10.1007/s00432-012-1330-z.

57. Ioanou K, Cheng KF, Crichlow GV, Birmpilis AI, LoLis EJ, Tsitsilonis OE, et al. ISO66, a novel inhibitor of macrophage migration inhibitory factor, shows efficacy in melanoma and colon cancer models. Int J Oncol. 2014;45:1457-1468. https://doi.org/10.3892/ijo.2014.2551.

58. Brown KK, Blaikie FH, Smith RA, Tyndall JD, Lue H, Bernhagen J, et al. Direct modification of the proinflammatory cytokine macrophage migration inhibitory factor by dietary isothiocyanates. J Biol Chem. 2009;284:32425-32433. https://doi.org/10.1074/jbc.M109.047092.

59. Dickerhof N, Magon NJ, Tyndall JD, Kettle AJ, Hampton MB. Potent inhibition of macrophage migration inhibitory factor (MIF) by myeloperoxidase-dependent oxidation of epicatechins. Biochem J. 2014;462:303-314. https://doi.org/10.1042/BJ20140612.

60. Spencer ES, Dale EJ, Gommans AL, Rutledge MT, Vo CT, Nakatani Y, et al. Multiple binding modes of isothiocyanates that inhibit macrophage migration inhibitory factor. Eur J Med Chem. 2015;93:501-510. https://doi.org/10.1016/j.ejmech.2015.02.012.

61. Bloom J, Sun S, Al-Abed Y. MIF, a controversial cytokine: a review of structural features, challenges, and opportunities for drug development. Expert Opin Ther Targets. 2016;20:1463-1475. https://doi.org/10.1080/14728222.2016.1251582.

62. Sakai Y, Masamune A, Satoh A, Nishihira J, Yamagiwa T, Shimosegawa T. Macrophage migration inhibitory factor is a critical mediator of severe acute pancreatitis. Gastroenterology. 2003;124:725-736. https://doi.org/10.1053/gast.2003.50099.

63. Matsuda N, Nishihira J, Takahashi Y, Kemmotsu O, Hattori Y. Role of macrophage migration inhibitory factor in acute lung injury in mice with acute pancreatitis complicated by endotoxemia. Am J Respir Cell Mol Biol. 2006;35:198-205. https://doi.org/10.1165/rcmb.2005-0272OC.

64. Sparkes A, De Baetselier P, Brys L, Cabrito I, Sterckx YG, Schoonooghe S, et al. Novel half-life extended anti-MIF nanobodies protect against endotoxic shock. FASEB J. 2018;32:3411-3422. https://doi.org/10.1096/fj.201701189R.

65. Hussain F, Freissmuth M, Völkel D, Thiele M, Douillard P, Antoine G, et al. Human anti-macrophage migration inhibitory factor antibodies inhibit growth of human prostate cancer cells in vitro and in vivo. Mol Cancer Ther. 2013;12:1223-1234. https://doi.org/10.1158/1535-7163.MCT-12-0988.

66. Mahalingam D, Patel MR, Sachdev JC, Hart LL, Halama N, Ramanathan RK, et al. Phase I study of imalumab (BAX69), a fully human recombinant anti-oxidized macrophage migration inhibitory factor antibody in advanced solid tumors. Br J Clin Pharmacol. 2020;86:1836-1848. https://doi.org/10.1111/bcp.14289.

67. Stein R, Qu Z, Cardillo TM, Chen S, Rosario A, Horak ID, et al. Antiproliferative activity of a humanized anti-CD74 monoclonal antibody, hLL1, on B-cell malignancies. Blood. 2004;104:3705-3711. https://doi.org/10.1182/blood-2004-03-0890.

68. Stein R, Smith MR, Chen S, Zalath M, Goldenberg DM. Combining milatuzumab with bortezomib, doxorubicin, or dexamethasone improves responses in multiple myeloma cell lines. Clin Cancer Res. 2009;15:2808-2817. https://doi.org/10.1158/1078-0432.CCR-08-1953.

69. Kaufman JL, Niesvizky R, Stadtmauer EA, Chanan-Khan A, Siegel D, Horne H, et al. Phase I, multicentre, dose-escalation trial of monotherapy with milatuzumab (humanized anti-CD74 monoclonal antibody) in relapsed or refractory multiple myeloma. Br J Haematol. 2013;163:478-486. https://doi.org/10.1111/bjh.12565.

70. Wallace DJ, Wegener WA, Horne H, Goldenberg DM. CT-01 Phase IB study of IMMU-115 (humanised ANTI-CD74 antibody) targeting antigen presenting cells in patients with systemic lupus erythematosus (SLE). Lupus Sci Med. 2016;3:A37. https://doi.org/10.1136/lupus-2016-000179.73.

71. Steinberg M, Silva M. Plerixafor: a chemokine receptor-4 antagonist for mobilization of hematopoietic stem cells for transplantation after high-dose chemotherapy for non-Hodgkin's lymphoma or multiple myeloma. Clin Ther. 2010;32:821-843. https://doi.org/10.1016/j.clinthera.2010.05.007.

72. Goldstein LJ, Perez RP, Yardley D, Han LK, Reuben JM, Gao H, et al. A window-of-opportunity trial of the CXCR1/2 inhibitor reparixin inoperable HER-2-negative breast cancer. Breast Cancer Res. 2020;22:4. https://doi.org/10.1186/s13058-019-1243-8.

73. Farr L, Ghosh S, Moonah S. Role of MIF cytokine/CD74 receptor pathway in protecting against injury and promoting repair. Front Immunol. 2020;11:1273. https://doi.org/10.3389/fimmu.2020.01273.

74. Harper JM, Wilkinson JE, Miller RA. Macrophage migration inhibitory factor-knock out mice are long lived and respond to caloric restriction. FASEB J. 2010;24:2436-2442. https://doi.org/10.1096/fj.09-152223.

75. Zhu C, Liu Y, Song Y, Wang Q, Liu Y, Yang S, et al. Deletion of macrophage migration inhibitory factor ameliorates inflammation in a mouse model of severe acute pancreatitis. Biomed Pharmacother. 2020;125:109919. https://doi.org/10.1016/j.biopha.2020.109919.

76. Kindt N, Preillon J, Kaltner H, Gabius HJ, Chevalier D, Rodriguez A, et al. Macrophage migration inhibitory factor in head and neck squamous cell carcinoma: clinical and experimental studies. J Cancer Res Clin Oncol. 2013;139:727-737. https://doi.org/10.1007/s00432-013-1375-7.

77. Funamizu N, Hu C, Lacy C, Schetter A, Zhang G, He P, et al. Macrophage migration inhibitory factor induces epithelial to mesenchymal transition, enhances tumor aggressiveness, and predicts clinical outcome in resected pancreatic ductal adenocarcinoma. Int J Cancer. 2013;132:785-794. https://doi.org/10.1002/ijc.27736.

78. Cisneros JA, Robertson MJ, Valhondo M, Jorgensen WL. A fluorescence polarization assay for binding to macrophage migration inhibitory factor and crystal structures for complexes of two potent inhibitors. J Am Chem Soc. 2016;138:8630-8. https://doi.org/10.1021/jacs.6b04910.

CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.