Macrophage Migration Inhibitor Factor As A Key Cytokine: Mechanisms Of Action And Its Role In Inflammatory And Autoimmune Disorders

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Abstract

Background and purpose: Macrophage migration inhibitory factor (MIF) is a versatile cytokine that is at the centre of immune regulation, connecting innate and adaptive immune responses and regulating inflammation, tissue remodelling and disease progression. Originally described as a macrophage-controlling factor, MIF is currently known to be a ubiquitously expressed cytokine that has context-specific roles in host defence, immune homeostasis and pathology. The review provides a critical analysis of the existing information on MIF signalling mechanisms and their role in chronic inflammation and autoimmune diseases.
Experimental method: The literature review was extensive, and it was based on the molecular biology of MIF, receptor-mediated signalling via CD74 and related chemokine receptors, and the downstream activation of PI3K/AKT, mitogen-activated protein kinase (MAPK), nuclear factor-KB (NF-KB), and inflammasome-related pathways. Experimental and clinical reports dealing with the role of MIF in inflammatory and autoimmune diseases were critically assessed.
Key findings: There is a growing body of evidence that MIF is a strong immunomodulatory mediator, which plays a role in the loss of immune tolerance and the maintenance of inflammation in a wide range of autoimmune diseases, including rheumatic, dermatological, endocrine, reproductive, and neurological diseases. Notably, tissue context and local immune architecture have a potent effect on the functionality implications of MIF signalling.
***Conclusion*:** MIF is an immunoregulatory centre of inflammatory and autoimmune pathology, which is very central but complicated. Although great progress has been made, there exist great gaps in knowledge. The selective and precise therapeutic modulation of MIF signalling will require the use of a systems-immunology framework.
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Keywords Immune dysregulation; Innate–adaptive immune crosstalk; Inflammatory signalling networks; Cytokine-mediated pathology; Immunomodulatory targets.

Introduction

Macrophage migration inhibitory factor (MIF) is a multifunctional cytokine that is at the centre of immune regulation, coordinating the innate and adaptive immune response and modulating inflammation, tissue homeostasis and pathogenesis of diseases [1]. MIF, first described as a T cell-derived factor that could block random migration of macrophages, was one of the first functional studies to show the regulation of macrophage activity via cytokines [2]. Later studies have determined that MIF is constitutively expressed in a large variety of cell types, such as immune cells, endothelial and epithelial cells, fibroblasts and neurons, highlighting its extensive biological applicability across various tissues and organ systems [3].

Though, MIF has been originally described as a pro-inflammatory mediator that supports the macrophage activation and cytokine production, subsequent research has shown that it has other functions outside of the classical inflammatory pathways. Under homeostatic conditions, MIF is involved in physiological host defence and is involved in tissue repair [4]. Moreover, it has been shown that MIF is also implicated in neuroprotective signalling, cardiovascular homeostasis and systemic adaptation to stress responses [5]. These protective functions are in addition to its pathogenic roles in chronic inflammation, immune dysregulation and tissue fibrosis, which promotes the idea of MIF as a Janus-faced cytokine with positive and negative biological functions depending on the setting [6].

MIF has pleiotropic effects at the molecular level by interacting with a wide range of receptor repertoire and activating a wide range of downstream signalling pathways. When MIF binds to its main receptor, CD74, intracellular cascades are triggered, which control the survival, migration, and release of cytokines in immune cells [7]. The interactions with co-receptors like CD44 and the chemokine receptors CXCR2, CXCR4 and CXCR7 often modulate these signalling responses and allow MIF to combine inflammatory and chemotactic signals in the population of immune cells [8]. When these pathways are chronically activated under immune-stimulated conditions, chronic activation of these pathways can induce MIF signalling to adopt pathogenic responses, leading to sustained inflammation and pathological tissue remodelling [9].

MIF has a pathological relevance, especially in chronic inflammatory diseases. MIF is involved in the maintenance of airway inflammation and structural remodelling in respiratory diseases, such as asthma and chronic obstructive pulmonary disease, in interactions with extracellular matrix-associated signalling pathways [10]. Dysregulated MIF expression has been linked to vascular inflammation, myocardial injury, and poor cardiac outcomes in the cardiovascular system [11]. Taken together, these results indicate the role of MIF in inflammatory tissue damage in a wide variety of organ systems and disease environments [12].

Another key setting where the pathogenic roles of MIF have become more and more clear is autoimmune disorders. MIF enhances autoimmune pathology by increasing inflammatory signalling, regulating the activation of macrophages and lymphocytes, and inhibiting glucocorticoid-mediated immunosuppression [13]. Higher levels of MIF expression and functionally relevant genetic polymorphisms have been associated with a higher risk of autoimmune disease and severity of disease, both rheumatoid arthritis and organ-specific autoimmune disease [14]. Persistent MIF signalling in rheumatic diseases is strongly linked with inflammation of the synovium and progressive joint erosion that is largely mediated by continued synthesis of inflammatory mediators in the inflamed tissues [15].

Literature Review

The recent achievements in immunology and molecular medicine have enhanced the knowledge about macrophage migration inhibitory factor (MIF) as a key immunoregulatory cytokine in a broad range of inflammatory, autoimmune, neuroinflammatory, cardiovascular, infectious and malignant illnesses [16]. Recent studies have been keen on highlighting the fact that MIF acts not only as a downstream pro-inflammatory effector, but also as an upstream regulator that can coordinate inflammatory signalling with extended immune control across multiple organ systems [17]. The accumulation of evidence proving that MIF can have a protective and pathogenic impact, depending on the context of the tissue, receptor interaction, and the duration of signalling activation, has motivated this reconceptualisation [18].

Recent synthesis reports further emphasise that MIF is to be considered a pleiotropic signalling molecule with far-reaching physiological implications [19]. In homeostatic conditions, MIF helps in immunosurveillance, stress adaptation, tissue repair, redox homeostasis, metabolic

homeostasis, and organ homeostasis [20]. Conversely, excessive or chronic MIF signalling facilitates chronic inflammation, immune pathology, fibrosis and tumour progression, which justifies its designation as a context-dependent Janus-faced cytokine [21]. Systems MIF has been found to influence innate and adaptive immune responses by sustaining cytokine networks, controlling immune cell traffic and altering macrophage and lymphocyte activation states [22].

MIF at the molecular level mediates its biological action by interacting with multicomponent receptor complexes. MIF binding to the cellular differentiation programme CD74, along with co-receptors like CD44 and the chemokine receptors CXCR2, CXCR4, and CXCR7, triggers intracellular signalling pathways, including PI3K/AKT, ERK/MAPK, and NF- 0- cascades [23]. These pathways control the survival, proliferation, migration and the generation of inflammatory mediators by immune cells. Chronic activation of these signalling networks in pathological contexts enhances immune responses, heightens resistance to suppressive processes, including glucocorticoid signalling and leads to chronic inflammatory and malignant disease phenotypes [24]. It is important to note that these signalling features are also seen in inflammatory and cancer-related pathologies, indicating that common molecular paradigms may define various pathological phenotypes [25].

There is an increasing literature that has highlighted the role of MIF in chronic inflammatory diseases. MIF has also been involved in chronic airway inflammation and remodelling of the airway in respiratory diseases like asthma and chronic obstructive lung disease by interacting with extracellular matrix-associated signalling pathways and the activation of inflammasomes [26]. High levels of MIF have been associated with vascular inflammation, myocardial injury, maladaptive cardiac remodelling and poor clinical outcome in cardiovascular disease, indicating its dual effect as both an agent of tissue injury and a therapeutic target [27]. In addition to sterile inflammation, extended or excess MIF signalling has also been linked to immune-mediated tissue damage in infectious and viral diseases, and it can also play a role in host defence and immunopathology [28] at the same time.

Autoimmune diseases are a significant clinical setting where the pathogenic effects of MIF are always evident. Experimental and clinical investigations indicate that MIF is often excessively expressed in autoimmune diseases and is closely linked to the severity of the disease, the presence of the inflammatory load, and tissue damage [29]. MIF contributes to synovial inflammation, macrophage activation, and fibroblast-like synoviocyte proliferation and progressive joint destruction in rheumatoid arthritis and other inflammatory rheumatic diseases via ERK- and PI3K/AKT-mediated mechanisms such as activation of matrix-degrading enzymes and production of prostaglands [30]. All of these processes cause long-term inflammation and structural damage that cannot be reversed.

The pathological significance of MIF is also evidenced by the organ-specific autoimmune diseases. MIF also enhances the severity of the disease in experimental autoimmune prostatitis by facilitating the activation of the PI3K/AKT pathway and NLRP3 inflammasome, which increases inflammatory signalling in the prostate microenvironment [31]. In pigmentary and inflammatory skin diseases, including vitiligo, dysregulated MIF signalling can change the effects of macrophages and increase the secretion of inflammatory mediators, which are associated with the melanocyte destruction and immune imbalance [32]. Equally, autoimmune thyroid diseases are also typified by macrophage-mediated inflammation and cytokine imbalance and MIF-related pathways seem to play a role in disease progression and thyroid tissue damage [33].

New evidence has also defined a significant role of MIF in neuroinflammatory and neurodegenerative diseases. MIF enhances the activation of microglia, astrocyte-mediated inflammation, neuronal damage, and the breakdown of the blood-brain barrier and connects systemic immune maladjustment to central nervous system pathology [34]. Moreover, genetic, transcriptomic, and causal inference analyses propose that peripheral immune tissue circulating inflammatory mediators, including MIF, can modulate the susceptibility to neurodegenerative disorders, including Parkinson disease and cognitive impairment, which is in line with the systemic applicability of MIF signalling [35].

In line with such disease-specific observations, MIF has become an attractive therapeutic target of translational research. Receptor antagonists, small-molecule inhibitors and novel proteolysis-targeting have been shown to be effective in preclinical models by suppressing inflammatory pathways, reprogramming macrophage phenotypes, and inhibiting disease progression in

autoimmune, inflammatory and malignant models via pharmacological inhibition of MIF signalling [36]. Moreover, MIF-associated pathways have been proposed as a potential target of drug repurposing studies, with artemisinin and its analogues having the ability to inhibit NF-KB-dependent inflammatory signalling and tumour-promoting pathways [37]. In addition, MIF, as well as its receptor CD74, has been suggested as a disease activity, prognosis, and therapeutic response biomarker, especially in oncology and immunomodulatory treatment settings [38].

Regardless of these developments, there are critical drawbacks. Most of the existing evidence is based on cross-sectional studies, disease-specific experimental models, or short-term interventions, which do not give much information on temporal relationships and long-term effects of MIF modulation [39]. The pleiotropic and context-dependent nature of MIF further complicates the problem of therapeutic targeting since non-selective inhibition can interfere with the protective immune, metabolic, and tissue-repair functions, as well as with pathogenic signalling pathways [40]. In turn, recent studies are more and more concerned with the necessity of precision-based, tissue-specific, and patient-stratified MIF-targeted therapy. Extensive literature on autoimmune and inflammatory diseases has shown that cytokine networks vary significantly in disease subtypes, disease stages, and organ settings, and that standardised cytokine blockade could be ineffective or even harmful in some types of patients [41,42]. Additionally, it has been shown that cytokine-mediated pathology depends on aetiology of disease, genetic factors, and immune compartments, and hence, the rationale of disease-specific therapeutic interventions, especially in neuroinflammatory and neurodegenerative diseases [43,44].

Oncological studies on pan-cancer analysis and tumour microenvironment also indicate that the expression and activity of MIF are highly context-dependent and affect the macrophage polarisation, immune suppression, angiogenesis, and responsiveness to treatment in tumour-specific ways [45]. These results suggest that MIF-focused therapies might require modification according to tumour type, immune infiltration state, and is being combined with other immunotherapies to provide significant clinical outcomes. Parallel to this, biomarker-based studies indicate that the levels of circulating and tissue-associated MIF, receptor expression patterns, and downstream signalling patterns can be used to assist in patient stratification and monitoring therapy [46]. Together, these data suggest that to establish effective clinical translation of MIF-based therapies, the combination of molecular, genetic, and immunological parameters will be necessary to establish the optimal balance between the inhibition of pathogenic signalling and the maintenance of protective homeostatic functions of MIF [47].

On the whole, the growing literature makes MIF the center of inflammation, autoimmunity, cancer, and neuroimmune disease with its key regulatory functions and its potential as a biomarker and a therapeutic target. More mechanistic, genetic, and translational discoveries will need to be incorporated in order to gain the therapeutic benefit of MIF modulation with the least amount of interference to its physiological actions.

Molecular Biology and Mechanisms of Action of Macrophage Migration Inhibitory Factor

The biological actions of macrophage migration inhibitory factor (MIF) are achieved by the combination of unique structural characteristics, receptor-mediated signalling and intracellular regulatory mechanisms, which altogether place it at the centre of immune response regulation. MIF is constitutively expressed and stored in preformed intracellular pools in contrast to many cytokines which are transcriptionally induced after immune stimulation thus allowing it to be released rapidly in response to inflammatory stimuli or stress-related signals. This property enables MIF to act as an early-response cytokine, which induces immune activation preceding the generation of classical inflammation-dependent transcriptional cascades. MIF is a protein with distinctive structural and functional properties such as homotrimer formation and enzymatic activity unlike traditional cytokines at the protein level.

MIF is the major ligand to the CD74 receptor that acts as a signalling hub by associating with co-receptors including CD44 and the chemokine receptors CXCR2, CXCR4, and CXCR7. It is the interaction of these multicomponent receptor complexes that allow MIF to combine the chemotactic and inflammatory messages, and thus, control the migration, activation, and survival of immune cells. MIF, on binding with the receptors, triggers a variety of intracellular signalling pathways, which are core to immune regulation. The phosphoinositide 3-kinase (PI3K)/AKT axis is one of the pathways that have been frequently involved. PI3K/AKT stimulation helps in survival

of immune cells, metabolic adjustment and production of inflammatory mediators. MIF-mediated PI3K/AKT signalling in autoimmune environments has been demonstrated to mediate NLRP3 inflammasome activation, which can be a mechanistic connection between MIF signalling and innate immune activation and chronic tissue inflammation.

Simultaneously, MIF triggers the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway, which is important in the growth of immune cells, the production of cytokines, and tissue remodelling. The literature on stromal-immune cell interactions shows that ERK downstream of MIF boosts the production of proinflammatory lipid mediators, such as prostaglandin E2, and thus facilitates fibrotic remodelling and chronic inflammation in the affected tissues [4]. Such findings indicate that MIF signalling is not confined to immune cells, but also exerts an enormous effect on non-immune stromal compartments that define inflammatory micro environments.

MIF regulates another key signalling axis, nuclear factor kappa B (NF- kB). MIF mediates long-term activation of NF-KB both via receptor-dependent and intracellular pathways leading to long-term expression of pro-inflammatory cytokines, chemokines, and survival-associated factors. Continued NF- kB signalling by MIF has been reported in chronic inflammatory and malignant diseases, where it plays a role in immune resistance and increased cellular survival to pathological stress [12]. The direction demonstrates that MIF has the ability to reverse endogenous anti-inflammatory responses and strengthen long-term immune response.

In addition to classical receptor-mediated signalling, it is becoming more and more evident that MIF is also an intracellular signalling network regulator. Phosphoproteomic studies have shown that MIF can modulate phosphorylation states in a variety of signalling nodes and suggest a more global role in the coordination of immune cell activation states, and not by discrete linear pathways. This kind of network-level regulation can be partially the reason behind the pleiotropy and context-dependency of MIF signalling.

The MIF activity has downstream effects that differ depending on the disease context. MIF signalling functions together with extracellular matrix-related molecules in respiratory inflammation to maintain airways inflammation and tissue remodelling. In the tumour microenvironment, MIF-mediated signalling enhances immunosuppression through polarisation of macrophages and suppression of infiltration of cytotoxic immune cells, and thus, immune evasion. Therapeutic inhibition of MIF signalling on the other hand has been demonstrated to reverse these effects, resulting in macrophage reprogramming and pro-survival signalling disruption in malignant cells [27].

All these mechanistic observations make MIF a multifunctional cytokine, which combines receptor-mediated signalling, intracellular regulation, and context-specific immune modulation. MIF can regulate immune cell activity, tissue remodelling and pathogenesis in a wide range of inflammatory, autoimmune and malignant disease through the coordinated activation of PI3K/AKT, ERK/MAPK, NF-kB and inflammasome-related signalling (Fig. 1).

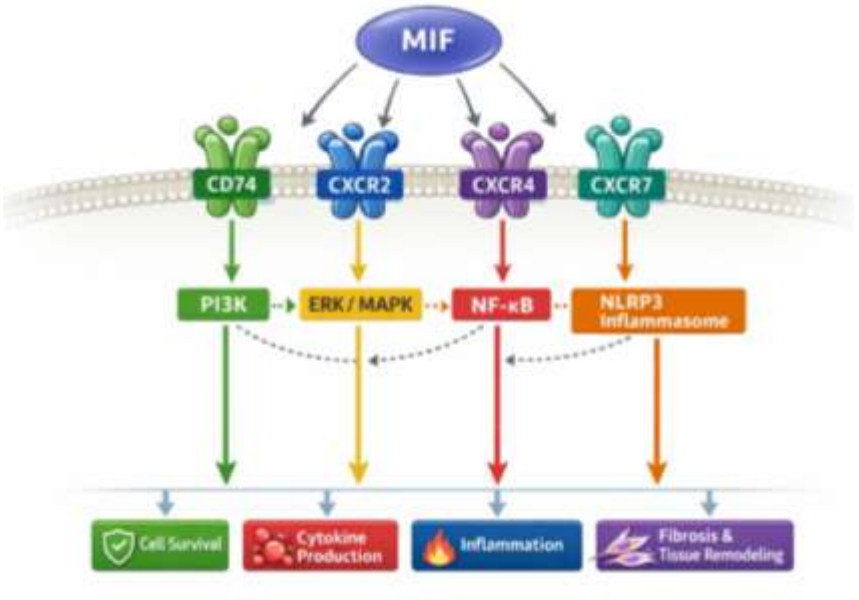


Figure 1 . Molecular and cellular signalling network of macrophage migration inhibitory factor (MIF).

Figure 1 demonstrates the major receptor-mediated signalling pathways which MIF triggers. MIF binding to CD74 and related chemokine receptors triggers coordinated signalling pathways that converge on PI3K/AKT, ERK/MAPK, NF- 0 B and inflammatory pathways. These interconnected networks maintain immune cell survival, increase cytokine production, maintain inflammatory responses and promote tissue remodelling in a variety of pathological settings through MIF.
Table 1 summarises the key MIF-activated signalling pathways and the cellular implications of this group of pathways under various disease conditions.

Table 1. Major MIF-Activated Signalling Pathways and Their Cellular Consequences

Signaling Pathway	Receptor Context	Primary Cell Types	Functional Outcome	Disease Context
PI3K/AKT	CD74–CXCRs	Macrophages	Survival, inflammasome activation	Autoimmune prostatitis
ERK/MAPK	CD74–CD44	Fibroblasts, immune cells	Proliferation, fibrosis	Joint & tissue remodelling
NF-κB	CD74 complex	Macrophages	Cytokine amplification	Chronic inflammation
NLRP3 inflammasome	Intracellular	Innate immune cells	IL-1β release	Autoimmune disease

Role of Macrophage Migration Inhibitory Factor in Inflammatory Disorders

The migration inhibitory factor (MIF) is a major mediator of the initiation, amplification, and maintenance of inflammatory responses in a wide spectrum of non-autoimmune inflammatory diseases. In contrast to the short-lived transient inflammatory mediators, which are downregulated in the resolution phase, MIF is a component of persistent inflammation as it strengthens immune activity and overcomes endogenous anti-inflammatory negative feedback. This chronic action makes MIF a significant cause of non-resolving inflammatory pathology in the various organ systems.

Respiratory disease is one of the most well characterised inflammatory situations that relates to MIF activity. In long-term airway diseases, such as asthma and chronic obstructive pulmonary disease, MIF is a contributor to long-term airway inflammation and tissue remodelling [3]. These are mediated by increased recruitment of inflammatory immune cells, sustained release of

cytokines and interference with extracellular matrix-related signalling pathways that affect tissue architecture. Together, these processes facilitate airway hyperresponsiveness and inhibit inflammatory resolution, which confirm the opinion that MIF is an amplifier of long-term respiratory inflammation, but not a short-term trigger of inflammation.

MIF also exhibits a duality of action in infectious and viral inflammatory diseases with its activities indicating the equilibrium of host defence and immunopathology. Though MIF has a role in early immune activation and control of pathogens, over stimulation or sustained stimulation has been linked to more inflammatory destruction [24]. The prolonged high levels of MIF in the course of viral infections might increase the production of cytokines and the activation of immune cells, thus facilitating the collateral tissue damage. This two-sided response highlights the context-dependent nature of MIF signalling where protective immune responses can change to pathological inflammation in case of failure in the regulatory mechanisms.

Another significant area where MIF has been found to be involved is cardiovascular inflammation. High MIF levels have been associated with vascular inflammation, endothelial dysfunction and maladaptive cardiac remodelling [25]. MIF facilitates the development of atherosclerosis and other inflammatory cardiovascular conditions through the stimulation of inflammatory signalling pathways and facilitation of immune cell invasion of vascular tissues. The interaction of pro-inflammatory cytokines also studies further implicate its role in chronic vascular inflammation and heart damage [46].

Fibrosis and structural tissue remodelling occur often with chronic inflammatory conditions and the emerging body of evidence suggests that MIF has a direct role in these events. MIF signalling has the potential to cause long-term activation of fibroblasts and stromal cells, increase deposition of extra cellular matrix, and long-term changes in tissue architecture. Such fibrotic reactions contribute to a positive feedback loop of inflammation and remodelling that is more difficult to reverse and as such prolongs the pathological action of MIF beyond immune control to progressive organ architecture and organ dysfunction.

MIF also has a role in localised, non-autoimmune inflammation, which is also seen in inflammatory diseases of the reproductive system. The role of MIF in inflammatory conditions of the gynaecological tract, such as endometriosis, has been observed in cytokine profiling studies, which revealed that MIF is a component of a long-term pro-inflammatory cytokine environment of chronic tissue inflammation and pain. Even though these disorders are characterized by complicated interplay between hormonal regulation and immune signalling, the existence of MIF in these networks further justifies its extended action as a perpetrator of chronic inflammation in non-classical immune tissues.

In a variety of inflammatory diseases, there is a consistent trend in which MIF acts as a sustained amplifier, which sustains inflammatory signalling after stimulation. MIF enhances the duration of inflammatory conditions by stimulating the production of cytokines, protecting the survival of immune cells, and reducing sensitivity to immune feedback, which is more effective than most other mediators. These characteristics indicate its possible usefulness as a therapeutic target too. MIF signalling inhibition could suppress chronic inflammation and restrain tissue remodelling, but since MIF has protective functions in acute host defence, therapeutic interventions should be designed to balance the inhibition of pathological signalling and maintenance of normal immune function [24,25].

Role of Macrophage Migration Inhibitory Factor in Autoimmune Disorders

The autoimmune diseases are caused by the loss of immune tolerance that results in chronic inflammation and progressive tissue damage. The central role in this process is played by cytokines that regulate the activation and differentiation of immune cells, as well as their functionality. MIF has been found as a significant mediator that enhances autoimmune pathology by acting in concert on innate and adaptive immune compartments. There is growing evidence to suggest that MIF is a context-dependent regulator which facilitates chronic inflammation, impairs immunoregulatory processes and maintains pathogenic immune circuits in a broad spectrum of autoimmune diseases.

Rheumatoid Arthritis and Rheumatic Diseases

The autoimmune contexts in which MIF has been implicated are some of the most widely studied rheumatoid arthritis and other inflammatory rheumatic disorders. These are diseases that are characterised by inflammation of the synovia, immune cell infiltration and progressive destruction

of the joints. High MIF levels are always linked to a high level of disease activity and inflammatory load, which confirms its pathogenic contribution to the development and progression of rheumatic diseases [21]. Mechanistically, MIF has a direct contribution to the pathology of the synovium by enhancing the activation of macrophages and maintaining the production of cytokines in the joint microenvironment. MIF signalling promotes long-term pro-inflammatory macrophage phenotypes, augmentation of the emission of inflammatory mediators, and lessening of responsiveness to regulatory feedback. Simultaneously, MIF affects the communication between the immune cells and stromal fibroblasts, thus promoting cartilage degeneration and bone erosion. Macrophage-mediated inflammation is a pathological axis that has remained dominant and macrophage phenotypic plasticity is becoming a central determinant of disease persistence and severity in rheumatic diseases.

Besides the impact on innate immunity, MIF also regulates adaptive immune responses in rheumatoid arthritis. It stimulates T-cell survival and activation and suppresses immunosuppression caused by glucocorticoids and maintains inflammatory activity despite therapeutic intervention [37]. The interplay of the effects of MIF on macrophages, lymphocytes, and stromal cells makes it a key mediator of chronic inflammation of the joints and structural tissue damage.

Specific Organ Autoimmune Diseases.

The value of MIF in immune pathology of tissues is also supported by evidence in organ-specific autoimmune diseases. In a model of experimental autoimmune prostatitis, MIF augments the disease severity through increasing the innate immune signalling pathways that stimulate local inflammatory responses [8]. In particular, MIF provokes the stimulation of the NLRP3 inflammasome via PI3K/AKT-signaling, which leads to the elevation of cytokine release and prolonged immune cells infiltration in prostate tissue. These results have a direct molecular connection between MIF signalling and inflammasome-mediated autoimmune inflammation.

MIF has also been involved in immune-mediated joint disorders as a result of its involvement in pathological immune-stromal interactions. Osteoarthritis models have indicated that MIF signalling enhances fibroblastB cell crosstalk that facilitates pathogenic B-cell population differentiation and leads to progressive joint destruction [22]. These observations define the functional role of MIF as more than the classical role of macrophage-mediated inflammation and underline the ability to organize multicellular immune networks in the target tissues.

Skin and Endocrine Autoimmunity.

The presence of cutaneous autoimmune disorders also shows that MIF has the pathogenic capability of mediating tissue-specific immune dysregulation. In vitiligo, an autoimmune disease, which is characterised by melanocyte destruction and loss of pigmentation, increased levels of MIF have been linked to altered macrophage activity and increased inflammatory signalling [10]. MIF facilitates the recruitment and activation of macrophages in the regions of the affected skin, which maintains a local inflammatory microenvironment that helps in the destruction of melanocytes. MIF expression is also associated with disease activity and clinical evidence indicates that it is relevant as a mediator of pathology and even as a biomarker of disease severity.

Another environment where MIF-related pathways mediating immune-mediated tissue damage are involved is endocrine autoimmune diseases, such as autoimmune thyroid disease. The autoimmune thyroiditis is defined by lymphocytic infiltration, macrophage activation and progressive destruction of thyroid. The dysregulation of cytokines and inflammatory processes mediated by macrophages are regarded as one of the key factors of the disease, and the MIF signalling can enhance the process of antigen presentation, cytokine generation, and the survival of immune cells in endocrine tissues [13].

Neurological Autoimmune and Neuroinflammatory Disorders.

Another growing field of research in MIF studies is neurological autoimmune and immune-mediated disorders. Neuroinflammatory diseases can be described as the activation and infiltration of microglia and peripheral immune cells, which result in the destruction of neurons and functional deficits. MIF is also found to induce neuroinflammation through the enhancement of microglial activation and the reinforcement of the inflammatory communication in the central nervous system [26]. Extensive neuroimmunological data also show that MIF-based cytokine networks play a role in disease susceptibility, disease progression and therapy response in autoimmune diseases of the nervous system [34,41]. Here, the signalling facilitated by MIF could

lead to immune persistence, defective mechanisms of immune resolution and could be the mechanism linking peripheral immune dysregulation to the pathology of the central nervous system.

Autoimmune Mechanisms Perspectives at the Systems Level.

In addition to models of diseases at an individual level, systems-level studies confirm the role of MIF as an important amplifier in autoimmune cytokine networks. The literature on the pathogenesis of autoimmune diseases has given a lot of attention to cytokine-mediated immune amplification, genetic predisposition, and environmental stimuli as key factors in the onset of autoimmune diseases and their progression [15,17,31]. MIF incorporates stress-related, immune, and metabolic signals in these networks, which result in persistent autoimmune inflammation. Massive profiling investigations of cytokines and growth factors also support the opinion that MIF is an important mediator of autoimmune disease activity and severity. These systems-based views underline the fact that MIF does not operate in isolation, but it is involved in interconnected cytokine networks, which together determine autoimmune pathology.

Summary

On the whole, the existing evidence recognises that MIF is a significant mediator in a variety of autoimmune diseases. MIF is able to enhance the effects of the inflammatory signalling, increase immune persistence, and promote progressive tissue destruction through coordinated actions on macrophages, lymphocytes, stromal cells, and tissue-resident immune populations. Although the extensive expression of MIF in several autoimmune diseases indicates that it should be considered a potential common therapeutic target, its tissue-specific activities also indicate that disease-specific approaches must consider the unique immune-tissue interactions in each pathological scenario.

In inflammatory and autoimmune diseases, MIF has been shown to have conserved immunomodulatory activity with varied pathological effects based on tissue microenvironment and the predominant immune cell types involved, as shown in Fig. 2.

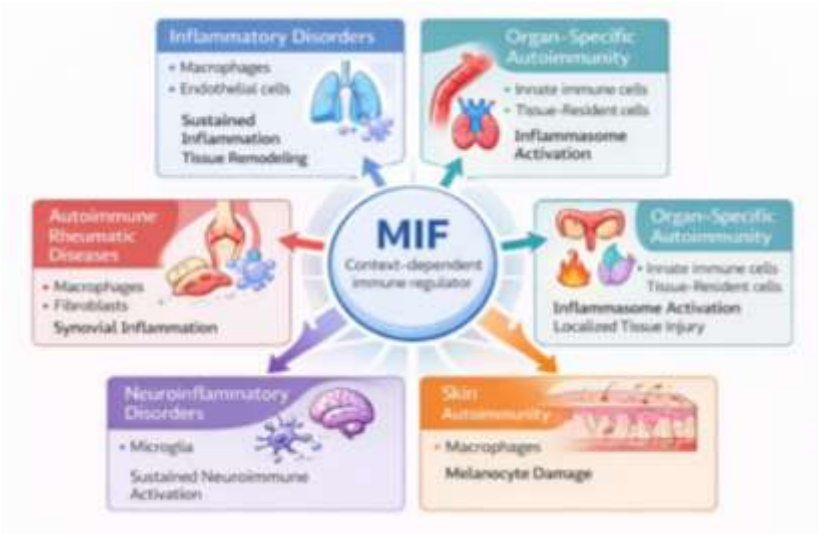


Figure 2. Context-dependent roles of macrophage migration inhibitory factor across inflammatory and autoimmune disease domains.

Figure 2 shows context-specific roles of MIF in the realms of inflammatory and autoimmune diseases, whereby disease-specific outcomes are highly dependent on the state of the tissues and the dominant cellular populations of the immune system. Despite the fact that MIF is a continuous stimulator of pro-inflammatory activity, the pathological effects are significantly different in rheumatic, organ-specific, cutaneous, and neuroinflammatory diseases.

Comparative Literature Analysis

The literature review has revealed that macrophage migration inhibitory factor (MIF) has both conserved and context-specific roles in inflammatory and autoimmune diseases. This

inconsistency underscores the significance of comparative appraisal in order to differentiate common mechanisms and disease specific roles. In non-autoimmune inflammatory diseases, MIF proves to have a comparatively preserved role in the preservation of chronic inflammation. MIF promotes immune cell activation and interactions with extracellular matrix-associated signalling pathways in persistent airway inflammation and tissue remodelling in respiratory diseases, including asthma and chronic obstructive pulmonary disease [3].

Likewise, in cardiovascular inflammation, MIF enhances the recruitment of immune cells, dysfunction of endothelium, and inflammatory remodelling of vascular tissues, which increases the progression of the disease [25,46]. MIF is also characterized by a dual role in inflammatory situations with viruses where it helps in the initial activation of the immune system but can worsen immunopathology when the signalling becomes persistent or deregulated. Although the aetiology of the disease differs, all these findings indicate that MIF is a persistence factor that inhibits the process of inflammatory resolution after the immune activation process has been initiated.

MIF has a greater role in the development of pathogenic immune circuits and tissue-specific injury in autoimmune disorders. MIF levels are linked to an augmented disease activity and joint ruination in rheumatoid arthritis and other rheumatic illnesses, which implies that it contributes to the maintenance of macrophage activation and inflammatory signalling in synovial tissues. MIF directly facilitates PI3K/AKT-dependent inflammasome activation in autoimmune prostatitis, which connects MIF signalling to innate immune amplification and tissue damage in the local area [8]. These data indicate that there is a change in generalised inflammatory persistence to more specific immune-mediated pathology in autoimmune conditions.

A significant factor that determines the MIF activity in various disease settings is cell-type specificity. In inflammatory diseases, macrophages are the main responders to MIF signalling and mediate the downstream effects such as cytokine secretion, immune cell recruitment and tissue remodelling [25]. Crosstalk between fibroblasts and B cells via MIF is however a pathogenic immune differentiation and progressive joint destruction in autoimmune joint disease. In cutaneous autoimmunity, e.g. vitiligo, MIF modulates macrophage activity in the skin microenvironment, which leads to the destruction of melanocytes and the development of the disease. These results also demonstrate that MIF signalling can be functionally plastic with regards to the preponderant immune and stromal cell type in particular tissues.

Further signs of MIF context dependency are also present in neurological and neuroinflammatory diseases. MIF in such environments enhances microglial stimulation and prolonged neuroimmune signalling thus connecting peripheral immune maladjustment and central nervous system pathology [26]. Wider neuroinflammatory research also shows that cytokine networks containing MIF also affect susceptibility and progression to disease and indicate systemic effects that go beyond traditional immune tissues [34].

Although there is a significant disease-specific variation, there are a number of mechanistic themes that are consistent. In inflammatory and autoimmune diseases, MIF signalling promotes the survival of immune cells, increases the pro-inflammatory responses, and decreases the efficiency of regulatory processes. Nevertheless, the ratio of protective and pathogenic impacts varies according to disease circumstances. MIF can have positive early host-defence effects in cardiovascular and viral inflammatory diseases but leads to pathological consequences in the long-term activation [24,25]. Conversely, in autoimmune diseases, MIF mostly strengthens already existing networks of pathogenic immunity and perpetuates inflammation once the disease has occurred [8,21]. Altogether, comparative evidence can be used to conclude that MIF is a central but highly versatile immunoregulatory cytokine. Its wide applicability in disease, and the difficulty of its therapeutic targeting, is indicative of its capacity to combine immune signalling in a variety of cellular and tissue settings. A comparative overview of MIF functions, cellular targets and dominant signalling pathways in disease settings is provided in Table 2.

Table 2. Comparative Roles of MIF Across Inflammatory and Autoimmune Diseases

Disease Context	Model Type	Dominant Cell Type	MIF Functional Role	Key Pathway / Mechanism	Reference

Asthma / COPD	Human & experimental	Macrophages, epithelial cells	Sustains airway inflammation and remodelling	Immune–ECM signalling	[3]
Viral inflammation	Clinical/experimental	Macrophages	Early immune activation; late immunopathology	Cytokine amplification	[24]
Cardiovascular inflammation	Clinical/experimental	Macrophages, endothelial cells	Vascular inflammation and remodelling	Pro-inflammatory cytokine signaling	[25], [46]
Rheumatoid arthritis	Clinical	Macrophages	Synovial inflammation and joint damage	Inflammatory macrophage activation	[21]
Autoimmune prostatitis	Experimental	Macrophages	Exacerbates autoimmune inflammation	PI3K/AKT–NLRP3 inflammasome	[8]
Osteoarthritis (immune-driven)	Experimental	Fibroblasts, B cells	Promotes pathogenic immune–stromal crosstalk	Fibroblast–B cell signalling	[22]
Vitiligo	Clinical	Macrophages	Enhances melanocyte destruction	Macrophage-mediated inflammation	[10]
Neuroinflammatory disorders	Experimental	Microglia	Sustains neuroimmune activation	Microglial inflammatory signalling	[26], [34]

Therapeutic Targeting of Macrophage Migration Inhibitory Factor

The key position of macrophage migration inhibitory factor (MIF) in maintaining inflammation, immune dysregulation, and disease progression has put it in the limelight as a promising therapeutic target in a spectrum of pathological diseases. Contrary to most of the cytokines, which are mainly downstream inflammatory mediators, MIF is an upstream enhancer of immune activation and survival signalling. Therefore, MIF therapeutic modulation can break early regulatory self-perpetuating inflammatory loops. The present-day options of MIF-targeting are direct inhibition of MIF activity, interruption of MIF-receptor interactions, and indirect regulation of MIF-related signalling pathways.

Small-Molecule Inhibitors of MIF

Small-molecule inhibition remains one of the most actively pursued strategies for targeting MIF. Structural and functional characterisation of MIF has enabled the development of compounds capable of disrupting its enzymatic activity and/or receptor binding. In particular, allosteric inhibitors of MIF have demonstrated the ability to suppress pathological cell survival and proliferation, especially in malignancies where MIF-dependent signalling contributes to tumour progression. These interventions interfere with pro-survival pathways and can induce cell cycle arrest, indicating that pharmacological targeting of MIF may exert direct disease-modifying effects. Beyond oncology, small-molecule MIF inhibitors have also been shown to modulate immune cell phenotypes and suppress inflammatory signalling. Experimental models of inflammatory and autoimmune disorders suggest that MIF inhibition reduces macrophage activation and limits cytokine production, supporting its relevance in macrophage-driven pathology. Importantly, available evidence indicates that MIF inhibition may promote immune reprogramming rather than

broadly suppressing immunity, distinguishing MIF-targeted strategies from conventional immunosuppressive therapies.

Antibody-Based and Receptor-Targeted Approaches

Another significant therapeutic approach to the inhibition of MIF signalling is the use of antibody-based interventions. Antibodies that neutralise MIF are meant to inhibit receptor and downstream signal transmission and thus limit its immunostimulatory activity. Simultaneously, the use of the main receptor of the MIF CD74 has become an attractive option, especially in the context of disease, where the MIF-CD74 pathway is a prevailing cause of immune dysregulation. Of interest is CD74-directed therapies in the oncology and immune-mediated disorders where MIF -CD74 signalling has been involved in immune evasion and therapy resistance. Interference with this pathway has been suggested as a direct treatment method as well as a form of sensitization to established immunotherapies. Since these methods target receptor-mediated signalling, it can be proposed that they will be more specific and less disruptive to intracellular or homeostatic activity of MIF.

Drug Repurposing and Indirect Modulation of MIF

Another approach to regulating MIF-related pathways is drug repurposing. Artemisinin and derivatives have shown potential in inhibiting inflammatory and tumour-promoting pathways that are related to MIF signalling. These agents have been demonstrated to suppress tumour growth and suppress immune activation implying therapeutic application in addition to their proven antimalarial uses. The possible repurposing of artemisinin derivatives in inflammatory and autoimmune diseases is further supported by further pharmacological research in which cytokine network modulation, including MIF-associated signalling, can be of clinical use. They have a proven clinical application and positive safety profile, which increase the interest in translation, but disease-specific dosage regimens and long-term treatment outcomes are not well established.

MIF as a Biomarker and Stratification Tool

Besides its usefulness as a therapeutic target, MIF and its signalling pathways are also becoming of interest as disease activity and treatment responsiveness biomarkers. MIF has been linked to severity of disease and immune suppression in various pathological conditions, which indicates that it could be used to stratify patients and make treatment decisions. MIF-CD74 signalling has also been suggested in the context of immunotherapy where it has been suggested as a marker of immune resistance, suggesting that MIF-targeted interventions can be used to predict or overcome treatment non-responsiveness. Taking into consideration the context-dependence of MIF signalling, biomarker-based methods can be especially significant in providing guidance to targeted therapy. By defining patient subsets where MIF is a prevailing pathogenic driver, more selective intervention can be achieved and the least amount of disturbance to protective immune processes.

Challenges and Translational Considerations

Although there is positive preclinical evidence, there are a number of difficulties in therapeutic targeting of MIF. The pleiotropic character of MIF poses the issue of off-target effect and unwanted interference of useful processes in host defence and tissue repair. Moreover, MIF inhibition worldwide can have different effects based on disease stage, tissue conditions and immune conditions.

In a more general sense, Cytokine-targeted therapies are often network effects, with blocking of one cytokine leading to the activation of other compensative inflammatory responses. These points indicate that context-sensitive interventions, combined treatment methods, and patient selection based on biomarkers are necessary in the design of MIF-targeted interventions.

Summary

In general, the therapeutic options to MIF involve direct inhibition, receptor blockage, drug repurposing strategies, and biomarker-based applications. Despite the preclinical evidence of the therapeutic potential of MIF modulation, the clinical translation will require the disease context, patient stratification, and immune network interactions complexity. The existing and novel approaches to targeting MIF signalling, along with some of the most important challenges in translation, are schematically outlined in Fig. 3.

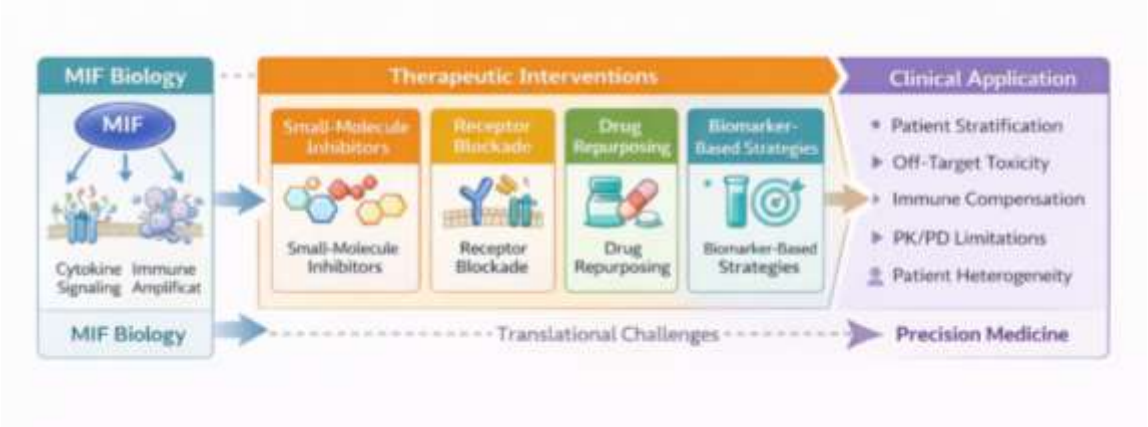


Figure 3. Translational Landscape of Targeting MIF in Inflammatory and Autoimmune Disorders

Figure 3 gives a summary of the existing and developing treatment approaches to MIF signalling and connects important mechanistic points of intervention to translational and clinical aspects. The schematic emphasises the potential limits of therapeutic efficacy due to patient heterogeneity, immune compensatory processes, and pharmacological constraints as the rationale to use more precise medicine approaches.

Table 3 provides a summary of representative strategies of therapeutic modulation of MIF signalling and their suggested uses in disease contexts.

Table 3. Therapeutic Approaches Targeting MIF Signalling: Mechanisms and Applications

Strategy	Modality	Target Level	Intended Effect	Disease Context
Small-molecule inhibitors	Chemical	MI enzymatic activity	Reduce inflammation	Cancer, autoimmunity
Allosteric inhibitors	Chemical	MIF conformation	Cell cycle arrest	Malignancy
Receptor blockade	Antibody	CD74/MIF axis	Immune reprogramming	Immune disorders
Drug repurposing	Small molecule	IndirectMIF suppression	Anti-inflammatory	Autoimmune disease
Biomarker use	Diagnostic	MIF/CD74 expression	Patient stratification	Immunotherapy

Pharmacological and Translational Considerations

Despite the fact that macrophage migration inhibitory factor (MIF) is an attractive therapeutic target, since it is a central mediator of immune amplification, pharmacological and translational development of MIF-directed interventions is still linked to significant challenges. These challenges are due to the pleiotropic nature of MIF, its role in various physiological events and the complexity of cytokine networks, which ensure immune homeostasis. In turn, to achieve successful clinical translation, it is essential to thoroughly consider the issues of drug-ability, pharmacokinetic and pharmacodynamic characteristics, safety rates, and patient stratification approaches.

Druggability and Target Accessibility

MIF has both positive and restrictive properties as a therapeutic target, pharmacologically. The extracellular signalling via specific receptor complexes offers a convenient target to intervention by neutralising antibodies, small-molecule inhibitors or receptor antagonists. Nevertheless, MIF also has intracellular activities that cannot be sufficiently covered using extracellular blockade. This bilateral localisation poses significant concerns on whether partial inhibition can be used to obtain therapeutic effects without affecting protective intracellular functions. There is already experience with cytokine-targeted therapies that selective modulation, that is designed to maintain immune homeostasis, as opposed to full inhibition, might be more suitable in most

disease contexts [41]. In this respect, selective interference with pathogenic MIF signalling, e.g. by receptor-specific or disease-adapted strategies, can have benefits over global suppression.

Pharmacokinetics, Pharmacodynamics, and Safety

The MIF-targeted therapies are of particular interest to pharmacodynamics (PD) and pharmacokinetics (PK) due to their rapid release kinetics, ubiquitous expression, and biological activity depending on the context. One of the issues is to attain sufficient target involvement without causing long-term systemic exposure which may enhance off-target effects. The use of short-acting agents, local delivery methods, or intermittent dosing schedule are some of the strategies that can be used to reduce systemic toxicity without compromising on the therapeutic effect. There is also pharmacological evidence of immunomodulatory compounds such as artemisinin derivatives which also suggests that dosing schedules should be optimised to achieve a balance between efficacy and safety [11,40]. These results help to justify the idea that immune modulation instead of general immunosuppression can be realised in case PK/PD parameters are properly adjusted to the context of a particular disease.

The issue of safety is also a primary translational issue as MIF is involved in host defence, tissue repair and stress adaptation. Random inhibition can thus impair positive immune activities, especially in a clinical situation where the immune activity varies with time. The more extensive exposure of cytokine-targeted therapies also emphasises the significance of long-term follow-up because immune resistance and the existence of redundancies in the pathways can decrease the duration of response and affect the long-term effects [41].

Patient Stratification and Precision Medicine

Another impediment to effective clinical implementation is patient heterogeneity. Not every patient with inflammatory or autoimmune disease has the same degree of pathology of the disease that is mediated by MIF. Changes in MIF expression, receptor availability and downstream signalling responsiveness can have a significant impact on therapeutic outcomes. Biomarker-based stratification of patients based on their activity of MIF would thus enhance clinical performance with limited exposure to targeted therapy.

The role of the alignment of immunomodulatory interventions with individual molecular and disease phenotypes is also becoming more and more significant in precision medicine frameworks [45]. In this strategy, MIF-targeted therapies can prove to be most effective in patient subgroups that are characterised by high MIF signalling or resistance to traditional anti-inflammatory therapies. Biomarker-guided selection will be vital in the clinical trial design to show the therapeutic value and those populations that have the highest probability of benefiting.

Summary

Altogether, to develop MIF-targeted therapies, pharmacological and translational development, there should be a careful balance between druggability, optimisation of PK/PD parameters, safety concerns, and patient heterogeneity. Notwithstanding the preclinical supportive nature of the MIF modulation, the therapeutic potential of MIF modulation must be successfully translated into clinical practice based on context-sensitive approaches, including selective targeting, patient stratification based on the biomarker, and systems-level knowledge of immune networks. These issues will also be important in the transition of MIF-targeted interventions between experimental models and effective clinical therapies.

Emerging Directions and Systems Immunology

Recent progress in systems immunology has led to a conceptual change in the way macrophage migration inhibitory factor (MIF) is viewed, and it is no longer an individual cytokine, but a part of a system of interconnected immune, metabolic and stress-response. There is a growing body of evidence that MIF can act as a nodal regulator that can integrate molecular signals on multiple biological layers, and thus affect the susceptibility and progression of disease in inflammatory and autoimmune diseases. Omics technologies have been used to offer significant understanding of the regulatory complexity of MIF signalling using high-throughput technologies.

Phosphoproteomic studies reveal that MIF does not only regulate discrete linear pathways but instead it is able to regulate the state of immune activation through broad networks of signalling, highlighting its ability to integrate state changes over time [6]. These results are in agreement with a systems-level model where MIF remodels the interactions between several signalling nodes, which strengthens immune persistence during chronic disease conditions. Immunometabolism is

also another important dimension that connects MIF with autoimmune pathology. As an example, the immunoregulatory metabolic intermediate itaconate is an example of a compound that regulates inflammatory responses and immune cell activity by modulating cross-talk functions between metabolic pathways and cytokine signalling pathways [29]. Combining MIF biology and immunometabolic regulation could thus help to explain the context-dependent immune effects and find new points of therapeutic intervention.

The interface of stress pathways and immune regulation can also be further increased to the relevance of MIF in systems immunology. Hypothalamic-pituitary-adrenal axis dysregulation and long-term stress exposure may cause immune homeostasis disruption and lead to autoimmunity, whereas MIF is the only hormone to reverse glucocorticoid-mediated immunosuppression [33]. This association gives a mechanistic connection between psychological stress, endocrine control and worsening of immune-mediated disease.

The methodologies of causal inference, such as the Mendelian randomisation, provide potent instruments to separate correlation and causation in the association of cytokines and diseases. Genetic studies indicate that inflammatory cytokines and MIF-related signalling pathways can be directly linked to vulnerability to autoimmune and neurodegenerative diseases [42]. Simultaneously, new studies on ferroptosis and iron homeostasis in immune cells indicate further control levels by which cytokine networks involving MIF can modulate autoimmune and autoinflammatory disease progressions [43].

All these systems-level views reiterate the importance of considering molecular, metabolic, genetic, and environmental aspects in order to gain a holistic view of the role of MIF in immune-mediated disease. These integrative methods will probably improve mechanistic understanding and help to create more accurate therapeutic methods.

Limitations and Knowledge Gaps

Although there has been significant progress in elucidating the biological roles of macrophage migration inhibitory factor (MIF), a number of critical limitations and gaps in knowledge remain to limit the translational and clinical progress. One of the biggest weaknesses of the available literature is that it is mostly cross-sectional and disease-specific. Though these studies have provided useful mechanistic information, they seldom reflect the temporal dynamics of MIF signalling in the initiation, progression and resolution of disease. The longitudinal studies in human populations are scarce, which limits the possibility of determining causality and differentiating protective and pathogenic effects of MIF over time.

The next important problem is the high level of heterogeneity of experimental models employed to study MIF biology. Variations in cells types, animal models, disease induction regimens and outcome measures make direct comparison across studies difficult and add to the variability of reported results. A notable level of heterogeneity is especially observed in inflammatory and autoimmune illnesses, in which the effects of MIF can be different depending on tissue microenvironment and immune composition. More standardisation of experimental paradigms would enhance the reproducibility and comparisons across diseases.

The translational gaps in the development of MIF-targeted therapies also exist. Despite the support of the therapeutic potential of MIF modulation by preclinical studies, there is little clinical validation. The pleiotropic characteristic of MIF is the basis of some valid questions on its safety, especially considering its functions in host defence, tissue repair, and stress adaptation. Moreover, long-term effects or possible immune compensatory responses are not sufficiently evaluated in many studies and it is hard to determine how long therapeutic responses can be sustained.

Patient heterogeneity is also a complication of clinical translation. The variance in the expression levels of MIF, patterns of receptor engagement and downstream signalling responsiveness indicates that only certain groups of patients are likely to respond to targeted interventions. Nonetheless, there are still no strong biomarkers that can reliably stratify patients based on the MIF-driven pathology.

Lastly, the application of MIF biology to larger systems immunology models has been in its infancy. It will be necessary to expand the use of multi-omics data, use causal inference methods, and network-level analyses to overcome the issue of context dependency, as well as to aid the rational design of therapeutic. It will be important to address these limitations in order to make MIF

research go beyond mechanistic characterisation to effective and clinically applicable therapeutic strategies.

Conclusion

Although significant progress has been made in elucidating the biological roles of macrophage migration inhibitory factor (MIF), a number of significant limitations and gaps in knowledge still limit both the translational and clinical development. The biggest weakness of the available literature is that most of the studies are cross-sectional and disease-specific. Though these studies have been able to provide important mechanistic information, they hardly reflect the temporal dynamics of MIF signalling in disease initiation, progression, and resolution. In human populations, longitudinal studies are still scarce and it is impossible to determine causality and differentiate between protective and pathogenic effects of MIF with time.

The other important issue is the high level of heterogeneity of the experimental models that are employed to study MIF biology. Variations in types of cells, animal models, protocols of inducing diseases and outcome measures make direct comparison of studies challenging and add to the variability of reported results. This heterogeneity can also be observed especially in inflammatory diseases and autoimmune diseases, where effects of MIF can be different depending on tissue microenvironment and immune constitution. The reproducibility and cross-disease comparisons would be enhanced by more standardisation of experimental paradigms.

MIF-targeted therapies are also associated with gaps in development. Despite the support of preclinical research regarding the therapeutic potential of MIF modulation, clinical validation has not been done extensively. The pleiotropic character of MIF also creates some serious doubts about its safety, especially considering its functions in host defence, tissue repair and stress adaptation. Also, long-term effects or possible immune compensatory mechanisms are not adequately evaluated in many studies, and therefore, it is challenging to foresee the sustainability of therapeutic responses.

Patient heterogeneity is also an additional complication of clinical translation. The difference in MIF expression levels, receptors engagement patterns, and downstream signalling responsiveness indicates the fact that only certain groups of patients are likely to respond to targeted interventions. Nevertheless, strong biomarkers that can categorise patients based on MIF-driven pathology with a high level of reliability are yet to be fully developed.

Lastly, MIF biology has not yet been integrated into larger systems immunology frameworks. It will be necessary to incorporate multi-omics data more widely, use causal inference methods, and network-scale analysis to overcome context dependency, as well as to aid rational therapeutic design. Overcoming these shortcomings will be essential in making MIF research a step forward in moving towards mechanistic characterisation to effective and clinically relevant therapeutic interventions.

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