

Macrophage Migration Inhibitory Factor and Pulmonary Immunity: A Systems Biology Perspective on Its Role in Lung Diseases

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ABSTRACT

Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that occupies a central regulatory position within pulmonary immune networks, integrating inflammatory signalling, redox control, and immune–stromal communication. Originally characterized as a proinflammatory mediator, MIF is now recognized to exert context-dependent functions that range from protective host defense during acute infection to pathogenic promotion of chronic inflammation, fibrosis, and tumor progression when regulatory constraints fail. This review synthesises current evidence on the molecular biology, structural features, and signalling mechanisms that govern MIF activity in the lung, emphasising its role as a network hub coordinating CD74/CD44- and CXCR-mediated signalling, glucocorticoid antagonism, and redox imbalance. A systems biology perspective is used to illustrate how genetic variability, environmental exposures, ageing, and metabolic stress reprogram MIF-centred immune circuits across pulmonary disease states. Integration of multi-omics insights, systems pharmacology, and computational modeling highlights emerging opportunities for precision modulation of MIF signaling rather than indiscriminate inhibition. Disease-specific manifestations of MIF dysregulation in pneumonia, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and lung cancer are discussed as dynamic outcomes of shared regulatory architectures. Collectively, this review positions MIF as a critical immunoregulatory node whose context-dependent modulation offers promising avenues for biomarker development and targeted therapeutic intervention in complex pulmonary disorders.

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1. Introduction

Respiratory disorders, including pneumonia, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and lung cancer, remain major contributors to global morbidity and mortality, particularly among ageing populations. Advancing age is accompanied by a progressive decline in immune competence and the emergence of chronic, low-grade inflammatory activity, commonly described as inflammaging. This persistent inflammatory milieu increases susceptibility to exaggerated immune responses and impairs tissue repair mechanisms, thereby creating conditions that favour the development and progression of chronic pulmonary disease. Disruption of immune homeostasis across multiple regulatory layers, rather than isolated molecular abnormalities, underlies these age-associated alterations, underscoring the need to elucidate integrative immunoregulatory mechanisms governing pulmonary immune balance.

Macrophage migration inhibitory factor (MIF) has emerged as a key regulator of both innate and adaptive immune responses and is now recognized as a multifunctional cytokine with broad biological influence. Originally identified for its ability to inhibit macrophage migration, MIF has since been shown to modulate inflammatory signaling, immune cell activation, metabolic regulation, and cellular stress responses. The functional versatility of MIF is strongly context-

dependent, enabling it to promote tissue protection under certain conditions while sustaining inflammatory signalling under others. Such versatility arises from its capacity to engage multiple receptor systems, including the CD74/CD44 complex and the chemokine receptors CXCR2, CXCR4, and CXCR7, through which inflammatory signalling pathways converge with mechanisms that control cell survival, migration, and proliferation (Harris et al., 2019). These interconnected signaling events position MIF as a central coordinator within pulmonary immune regulation.

In addition to its immunomodulatory functions, MIF serves as a critical link between metabolic stress, redox balance, and inflammatory activation. Through its involvement in glucocorticoid resistance, macrophage activation, and intrinsic tautomerase and oxidoreductase activities, MIF influences oxidative equilibrium and reinforces inflammatory signalling cascades. Sustained or dysregulated expression of MIF has been associated with chronic inflammatory states characterized by persistent cytokine production, leading to maladaptive tissue remodeling and fibrotic progression in age-related pulmonary disorders (Abbas, 2026). Observations from neuroinflammatory conditions further demonstrate that MIF signaling may exert divergent effects depending on cellular and molecular context, underscoring the importance of regulatory interactions and signaling dynamics in determining biological outcomes (Petrulia et al., 2020). Moreover, the conformational flexibility of MIF enables interactions with diverse intracellular partners, contributing to its pleiotropic effects and broad systemic influence (Leyton-Jaimes et al., 2018).

Given its capacity to integrate inflammatory, metabolic, and redox-related signals, MIF plays a decisive role in shaping pulmonary immune behavior and disease trajectories. This review synthesises current evidence on MIF biology, with an emphasis on its molecular architecture, receptor-mediated signalling integration, redox regulation, and immunopathological relevance in lung diseases. By consolidating mechanistic insights with clinical observations, the review aims to clarify how coordinated MIF-driven regulatory interactions contribute to the initiation and progression of pulmonary disorders, and to critically evaluate the potential utility of MIF as a biomarker and therapeutic target in precision respiratory medicine.

2. Molecular Biology and Structural Basis of MIF

2.1 Gene Organization and Polymorphisms

The MIF gene on chromosome 22q11.2 encodes a highly conserved 12.5 kDa protein. Promoter polymorphisms, notably the tetranucleotide CATT repeat and the −173 G/C single-nucleotide polymorphism, regulate transcriptional activity and circulating MIF levels, thereby shaping inter-individual immune responsiveness (Bucala & Bernhagen, 2017). High-expression variants, such as CATT7–8 repeats and the −173 C allele, enhance MIF transcription and are associated with hyperinflammatory phenotypes, glucocorticoid resistance, and impaired immune resolution. Sustained MIF elevation driven by these variants reinforces macrophage activation and redox imbalance, promoting chronic inflammatory and fibrotic lung disease, including COPD, asthma, and idiopathic pulmonary fibrosis. Key MIF gene variants and their disease associations are summarized in Table 1.

Table 1: Key MIF Gene Variants and Their Functional Links to Respiratory Disease Susceptibility

Polymorphism	Genomic Location	Functional Effect	Associated Condition	Clinical Implication / Supporting References
-794 CATT5-8	Upstream Promoter	High-repeat alleles (CATT7-8) increase MIF transcriptional activity	Pulmonary fibrosis, tuberculosis, sepsis-induced ARDS	Predicts severe inflammation and fibrosis progression (Illescas et al., 2018; Leng et al., 2019)
-173 G/C	Promoter Region	Enhances MIF transcription via altered AP-4 binding	COPD, asthma, familial Mediterranean fever	Elevated inflammatory response and poor steroid responsiveness (Flores-Sampedro et al., 2020)
rs755622	Promoter	Regulates MIF secretion and receptor interaction	Idiopathic pulmonary fibrosis, autoimmune and inflammatory diseases	Genetic susceptibility to fibrogenesis and dysregulated cytokine release (Cebulla et al., 2019; Hizawa et al., 2004)
rs2070766	Intron 1	Alters splicing efficiency and mRNA stability	Lung cancer	Potential diagnostic biomarker for tumour progression (Ma et al., 2018)
rs1007888	3'-UTR	Modulates the post-transcriptional regulation of MIF mRNA	Asthma, COPD	Influences response to MIF-targeted therapies and immune regulation (Cakan et al., 2022)

2.2 Protein Structure and Catalytic Motifs

MIF forms a homotrimeric structure in which each monomer contributes to a central catalytic pocket responsible for tautomerase and oxidoreductase activity (Kok et al., 2018). Catalytic residues, including Pro¹ and Lys³², regulate thiol-disulfide exchange and the balance of reactive oxygen species, thereby enabling redox-sensitive immune modulation. This trimeric architecture also governs interactions with CD74/CD44 and the chemokine receptors CXCR2, CXCR4, and CXCR7,

thereby linking molecular conformation to immune cell recruitment and survival signalling (Trivedi-Parmar & Jorgensen, 2018). These structure–function relationships are illustrated in Figure 1.

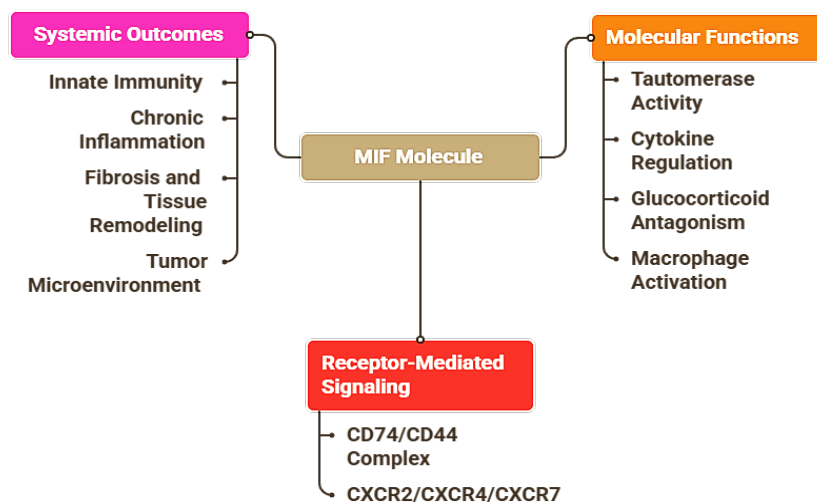


Figure 1: Overview of the Macrophage Migration Inhibitory Factor (MIF) Molecule and its Systemic Effects

2.3 Advances in Inhibitor Design and Structural Modulation

Medicinal chemistry efforts have identified MIF antagonists such as ISO-1, 4-IPP, and benzoxazole or isoxazole analogues that covalently target the tautomerase active site and suppress downstream inflammatory and fibrotic signaling (Guo et al., 2025). These inhibitors also disrupt MIF engagement with CD74/CD44, restoring corticosteroid sensitivity in resistant airway inflammation. Optimisation strategies emphasise pulmonary bioavailability, metabolic stability, and tissue selectivity via inhalable and nanoparticle-based delivery systems to locally recalibrate MIF-driven immune networks while limiting systemic effects.

2.4 Cellular Sources and Regulation of Expression

MIF is constitutively expressed by macrophages, T lymphocytes, airway epithelial cells, and endothelial cells and is rapidly released in response to infection, oxidative stress, or hypoxia (Fan et al., 2020). Lack of a classical signal peptide enables rapid secretion and redistribution within the alveolar microenvironment. Environmental exposures such as cigarette smoke and ozone further amplify MIF expression, reinforcing immune activation. While this supports host defense, persistent overexpression stabilizes maladaptive inflammatory states that drive tissue remodeling and functional decline (Husebø et al., 2016).

2.5 Clinical Relevance of MIF Expression in Pulmonary Disorders

Elevated circulating and alveolar MIF levels correlate with disease severity in COPD and idiopathic pulmonary fibrosis, reflecting sustained immune activation and regulatory imbalance (Bargagli et al., 2009). In COPD, MIF promotes macrophage and neutrophil recruitment, whereas in fibrotic disease it drives fibroblast activation and extracellular matrix deposition. These patterns indicate that MIF expression mirrors systemic immune dysregulation rather than isolated inflammation, positioning MIF as both a biomarker and a therapeutic target requiring lung-selective, pharmacokinetically optimized intervention (Jalce & Guignabert, 2020).

3. Signalling Pathways and Molecular Mechanisms

3.1 MIF Receptor Systems: CD74/CD44 Complex and Chemokine-Like Signaling

Macrophage migration inhibitory factor (MIF) mediates its cellular effects through multiple receptor systems, most prominently the CD74/CD44 complex. CD74 serves as the primary high-affinity receptor, and MIF binding promotes recruitment of CD44, initiating downstream MAPK/ERK and PI3K/Akt signaling pathways that regulate cell survival, proliferation, and cytokine production (Lan et al., 2018). This integrated signalling axis links immune activation to structural responses within pulmonary tissue.

In the lung, activation of ERK1/2 and focal adhesion kinase (FAK) in endothelial and smooth muscle cells promotes

cellular proliferation and migration, and alters vascular tone, contributing to vascular remodelling and pulmonary hypertension (Lan et al., 2020). In parallel, MIF acts as a non-cognate ligand for chemokine receptors CXCR2, CXCR4, and CXCR7, enhancing leukocyte chemotaxis, neutrophil recruitment, and monocyte adhesion. Signalling through both cytokine and chemokine receptor systems enables coordinated communication between immune and structural compartments, thereby driving airway remodelling, vascular inflammation, and fibrotic progression in chronic lung disease (Ahmed & Miller, 2018). Collectively, this dual receptor engagement positions MIF as a central coordinator of pulmonary immune dynamics, as illustrated in Figure 2.

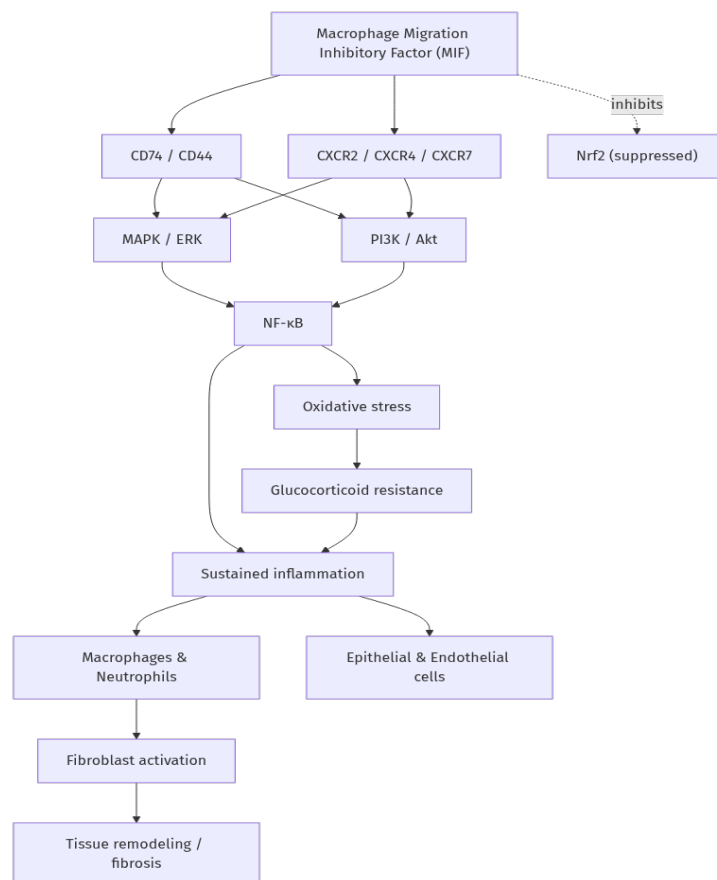


Figure 2: MIF-Centered Pulmonary Immune Network Map

3.2 Crosstalk with Glucocorticoid Signaling

A defining feature of MIF biology is its antagonistic interaction with glucocorticoid signaling. Unlike most cytokines, MIF expression is induced by glucocorticoids and subsequently counteracts their anti-inflammatory effects, sustaining inflammation despite corticosteroid therapy (Chen et al., 2020). MIF inhibits MAPK phosphatase-1 (MKP-1), thereby preserving p38 and ERK activation and prolonging cytokine production (Fan & Fan, 2018). Additionally, MIF interferes with glucocorticoid receptor nuclear translocation and DNA binding, further limiting glucocorticoid-mediated gene repression. Clinically, MIF-driven glucocorticoid resistance correlates with persistent macrophage activation, elevated oxidative stress, and poor therapeutic responsiveness in severe asthma, COPD, and ARDS (Aegerter et al., 2022). These mechanisms highlight MIF signaling as a key target for restoring steroid sensitivity in treatment-refractory pulmonary inflammation.

3.3 Regulation of Oxidative and Redox Pathways

Oxidative stress is a hallmark of chronic pulmonary inflammation, and MIF plays a central role in redox regulation. Through intrinsic oxidoreductase activity mediated by conserved cysteine and proline residues, MIF participates in thiol-disulfide exchange and in the control of reactive oxygen species (ROS) under physiological conditions (Bueno et al., 2015). Sustained MIF expression, however, shifts redox balance toward oxidative amplification by promoting NADPH oxidase activation and mitochondrial dysfunction. MIF enhances NF-κB activation, increasing expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while concurrently suppressing Nrf2-mediated antioxidant responses (Checa & Aran, 2020; Mehta et al., 2020). Environmental stressors, including cigarette smoke, ozone, and particulate pollutants,

further amplify these effects by increasing MIF expression, reinforcing a feed-forward loop linking oxidative stress and inflammation (Mumby et al., 2019).

3.4 Downstream Immune Modulation and Macrophage Polarization

MIF exerts broad downstream effects on immune regulation, with macrophage polarization representing a central effector mechanism. MIF promotes a pro-inflammatory M1 phenotype characterized by enhanced nitric oxide production, cytokine release, and antigen presentation, contributing to epithelial injury and barrier disruption in acute and chronic lung disease (Wiegman et al., 2020). Simultaneously, MIF suppresses M2 polarisation by limiting STAT6- and IL-10-dependent signalling, thereby delaying tissue repair and resolution.

MIF also enhances T-cell activation and supports neutrophil recruitment via CXCR2 and CXCR4, generating a tightly coupled inflammatory network involving epithelial cells, macrophages, and neutrophils. In chronic pulmonary disorders such as COPD, asthma, and pulmonary fibrosis, these interactions sustain immune activation and drive progressive tissue remodeling (Ma et al., 2019). The coordinated effects of receptor engagement, glucocorticoid antagonism, and redox dysregulation are summarised in Figure 3, and key MIF-regulated signalling modules and functional outcomes are presented in Table 2.

Table 2: MIF-Regulated Signaling Modules and Functional Outcomes in Pulmonary Immunity

Signaling Module	Primary Receptors	Key Downstream Mediators	Dominant Cell Types	Functional Outcome
Inflammatory Activation Module	CD74/CD44	ERK, p38, NF- κ B	Macrophages, epithelial cells	Sustained cytokine release
Chemotactic Recruitment Module	CXCR2/CXCR4	FAK, PI3K/Akt	Neutrophils, monocytes	Immune cell infiltration
Redox Imbalance Module	CD74-dependent	ROS, Nrf2 suppression	Epithelial cells	Oxidative injury
Steroid Resistance Module	CD74/CD44	MKP-1 suppression	Macrophages	Corticosteroid insensitivity
Remodeling/Fibrosis Module	CXCR4/CXCR7	TGF- β signaling	Fibroblasts	Tissue remodeling

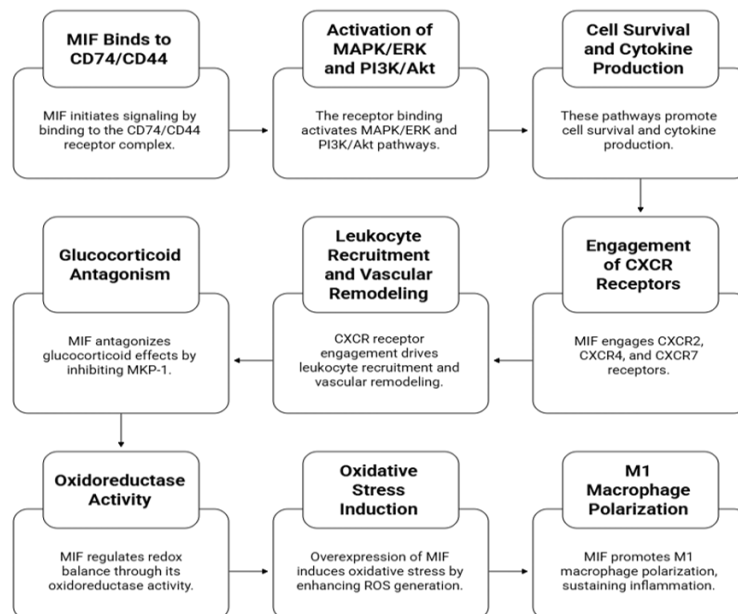


Figure 3: Integrated Signalling Pathways of Macrophage Migration Inhibitory Factor (MIF) in Pulmonary Inflammation

4. MIF in Pulmonary Immunity and Host Defence

4.1 Role in Innate Immune Responses

Macrophage migration inhibitory factor (MIF) plays a central role in innate immune defence by coordinating macrophage activation, phagocytosis, and the production of inflammatory mediators. In the pulmonary environment, MIF amplifies early host responses to infection by enhancing pathogen recognition and microbial killing. During intracellular

infections such as *Mycobacterium tuberculosis*, rapid induction of MIF in alveolar macrophages supports effective immune clearance, whereas impaired bactericidal activity in MIF-deficient macrophages underscores the importance of MIF in pulmonary host defence. MIF enhances phagocytosis by upregulating scavenger receptors and Toll-like receptor (TLR) signalling, particularly TLR2 and TLR4, thereby optimising pathogen elimination.

Beyond macrophages, MIF regulates neutrophil recruitment through CXCR2- and CXCR4-dependent chemotactic mechanisms, facilitating immune cell trafficking to inflamed alveolar regions (Li et al., 2024). Although essential for early microbial control, excessive neutrophilic infiltration contributes to tissue injury. MIF-driven neutrophil accumulation has been implicated in acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury, where amplified cytokine release disrupts alveolar barrier integrity and increases vascular permeability (de Souza et al., 2019). By regulating upstream cytokines such as TNF- α , IL-6, and IL-8, MIF coordinates inflammatory amplification loops during acute lung inflammation.

MIF further modulates the balance between pro- and anti-inflammatory mediators, influencing IL-10 and IL-1 receptor antagonist signaling to fine-tune immune intensity. While controlled activation supports effective defense, dysregulated signaling promotes cytokine storm development and pathological inflammation (Nieto-Fontarigo et al., 2019). Through these mechanisms, MIF serves as a key intermediary linking innate immune surveillance to adaptive immune engagement in pulmonary infections.

4.2 Adaptive Immune Modulation

MIF exerts broad regulatory control over adaptive immunity by influencing T-cell differentiation, antigen presentation, and immune tolerance. It promotes Th1 polarization through IL-12 and IFN- γ signaling while suppressing Th2-associated cytokines such as IL-4 and IL-10, thereby enhancing antimicrobial defense (Bianco et al., 2019). However, sustained Th1-skewed responses contribute to chronic inflammatory injury in pulmonary disease. In parallel, MIF enhances IL-6 and IL-23 signaling, facilitating Th17 differentiation and reinforcing proinflammatory cytokine cascades, resulting in a Th1/Th17-dominated immune milieu in asthma, COPD, and interstitial lung disease.

MIF also enhances antigen-presenting cell function by upregulating MHC class II molecules and costimulatory markers CD80 and CD86 on dendritic cells and macrophages, promoting T-cell priming and clonal expansion. Persistent MIF signaling, however, disrupts immune tolerance and predisposes pulmonary tissues to prolonged T-cell activation and autoimmune-like responses (Naccache et al., 2018).

In lung cancer, MIF contributes to immune evasion by promoting tumour-associated macrophage polarisation toward immunosuppressive phenotypes and facilitating the recruitment of myeloid-derived suppressor cells via the MIF-CD74 axis. These mechanisms suppress cytotoxic T-cell activity and reduce responsiveness to immune checkpoint inhibition, while accelerating fibrotic remodeling in patients with coexisting interstitial lung disease and lung cancer. MIF-driven macrophage polarisation and microRNA-mediated signalling further influence fibroblast activation and extracellular matrix deposition, thereby linking immune dysregulation to pathological tissue remodelling.

4.3 MIF and the Ageing Lung Immune Environment

With advancing age, MIF becomes closely associated with immunosenescence and altered cytokine dynamics in the lung. Ageing tissues exhibit chronic low-grade inflammation marked by elevated proinflammatory cytokines and diminished regenerative capacity. MIF sustains macrophage activation and delays inflammatory resolution, while age-associated hypersensitivity of alveolar macrophages promotes excessive reactive oxygen species production and inflammatory mediator release, accelerating epithelial injury and matrix accumulation (Kishore & Petrek, 2021).

Chronic elevation of MIF in elderly individuals correlates with increased expression of fibrotic markers, including collagen I and fibronectin. Persistent activation of the MIF-CD74 and MIF-CXCR4 signalling pathways enhances fibroblast proliferation and myofibroblast differentiation, thereby accelerating fibrotic progression. Age-related immune remodelling also includes the depletion of naïve T cells and the accumulation of senescent T cells expressing exhaustion markers such as PD-1 and TIM-3, thereby impairing immune surveillance and adaptive responsiveness. MIF-driven persistence of fibrogenic mediators, including TGF- β and IL-13, reinforces tissue stiffening and disease progression. Pharmacological inhibition of MIF or CD74 has demonstrated potential in reducing fibroblast activation and collagen deposition, partially restoring pulmonary function (Datta et al., 2011).

Overall, MIF acts as both a protective and disruptive regulator of pulmonary immune balance across the lifespan. While essential for early defense and repair, sustained MIF signaling during ageing promotes chronic inflammation, immune exhaustion, and fibrotic remodeling. Through coordinated modulation of macrophage activity, T-cell dynamics, and immune-stromal interactions, MIF serves as a central link between ageing, immunity, and chronic lung pathology. An integrated overview of MIF-mediated regulation of pulmonary innate and adaptive immune responses is summarized in Figure 4.

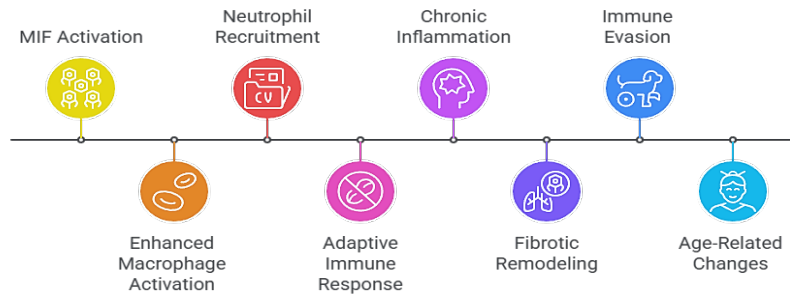


Figure 4: MIF's Role in Pulmonary Immunity

4.4 MIF in Specific Pulmonary Diseases

MIF functions as an upstream immunoregulatory mediator integrating inflammatory signaling, oxidative stress, and immune modulation across diverse pulmonary diseases. Rather than acting as a disease-specific cytokine, MIF regulates shared immune mechanisms that manifest as distinct pathological phenotypes depending on tissue context and disease stage. Through coordinated effects on innate and adaptive immunity, MIF shapes host defence and chronic pathological remodelling in the lung. Disease-specific patterns of MIF-driven immune dysregulation in pneumonia, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and lung cancer are summarised in Figure 5, illustrating how shared signalling architectures can generate divergent clinical outcomes.

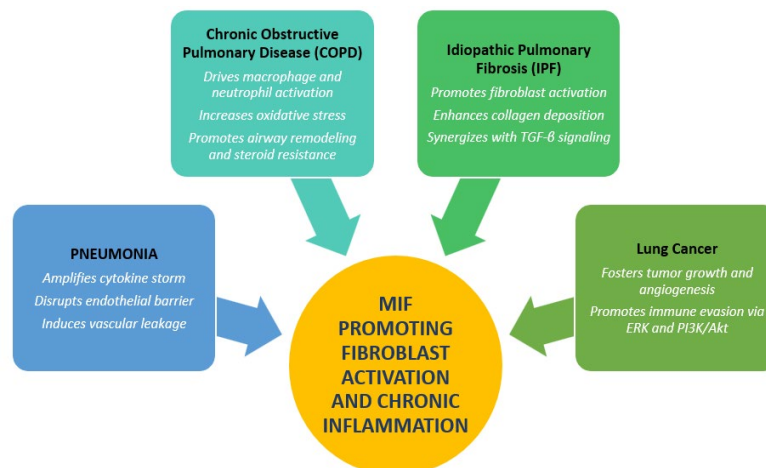


Figure 5: Disease-Specific Pathogenic Roles of Macrophage Migration Inhibitory Factor (MIF) in Pulmonary Disorders

4.5 Pneumonia and Acute Respiratory Distress Syndrome (ARDS)

During acute pulmonary infection, MIF expression rapidly increases in alveolar macrophages and endothelial cells, amplifying cytokine cascades and leukocyte recruitment. Sustained MIF signalling enhances NF- κ B activation and disrupts epithelial–endothelial barrier integrity, resulting in increased vascular permeability, alveolar oedema, and a cytokine storm. Experimental inhibition of MIF attenuates inflammatory severity and pulmonary permeability, underscoring its role in immune overactivation during pneumonia and ARDS (Günther et al., 2019). In bleomycin-induced injury models, MIF blockade limits fibroblast activation and collagen accumulation, suggesting that early inflammatory dysregulation may predispose to later fibrotic remodeling. Targeted pulmonary modulation of MIF may therefore reduce acute injury while preserving antimicrobial defense.

4.6 Chronic Obstructive Pulmonary Disease (COPD)

In COPD, persistent MIF overexpression within airway macrophages and epithelial cells reinforces oxidative stress and glucocorticoid resistance. Activation of the MAPK and PI3K/Akt signalling pathways promotes macrophage survival and sustained neutrophil recruitment, thereby maintaining chronic inflammation (Plichta et al., 2023). Genetic variants that enhance MIF transcription contribute to inter-individual variability in inflammatory burden and therapeutic responsiveness. Elevated MIF activity correlates with reduced corticosteroid efficacy, while pharmacological inhibition restores steroid sensitivity and reduces oxidative injury (Arora et al., 2024). Optimization of lung-targeted delivery strategies may further

improve long-term disease control.

4.7 Idiopathic Pulmonary Fibrosis (IPF)

In fibrotic lung disease, MIF mediates the link between immune activation and fibroblast proliferation, driving progressive tissue remodelling. Through ERK and focal adhesion kinase signaling, MIF promotes myofibroblast differentiation and epithelial–mesenchymal transition, disrupting alveolar repair (Brewer et al., 2025). Synergistic interactions with profibrotic mediators such as transforming growth factor- β amplify extracellular matrix synthesis. Nanocarrier-based delivery of MIF inhibitors and regulatory microRNAs improves lung retention and targeted biodistribution, highlighting the importance of controlled immune–stromal modulation in attenuating fibrosis while preserving immune competence (Kumar et al., 2018).

4.8 Lung Cancer

Within the pulmonary tumor microenvironment, MIF promotes angiogenesis, immune evasion, and tumor progression through sustained ERK and PI3K/Akt signaling. Elevated MIF expression promotes the recruitment and polarisation of tumour-associated macrophages toward immunosuppressive phenotypes while inhibiting cytotoxic T-cell activity, thereby facilitating tumour growth and metastasis. Pharmacological inhibition of MIF reduces tumor burden and metastatic potential in experimental models (Charan et al., 2020). Combinatorial strategies integrating MIF antagonists with immune checkpoint inhibitors may enhance antitumor immunity, provided adequate pulmonary distribution and metabolic stability are achieved.

Across pulmonary pathologies, MIF emerges as a central regulatory node integrating cytokine signaling, oxidative imbalance, and immune tolerance. Context-dependent modulation of MIF activity determines whether immune responses remain protective or progress toward chronic inflammation, fibrosis, or immune escape. Therapeutic targeting of MIF therefore offers the potential to restore immune equilibrium and enhance responsiveness to existing treatments while minimizing systemic toxicity.

5. Dual Role of MIF: Protective vs. Pathogenic

5.1 Context-Dependent Effects of MIF

Macrophage migration inhibitory factor (MIF) displays marked functional duality, acting as a protective mediator or a driver of pulmonary pathology depending on inflammatory context and disease stage. Transient MIF induction during acute infection or tissue injury enhances host defense by promoting leukocyte recruitment, macrophage activation, and pathogen clearance, thereby supporting immune containment and tissue repair. In contrast, sustained or dysregulated MIF expression shifts immune regulation toward chronic inflammation, fibrosis, and tissue damage through persistent activation of immune and redox signaling networks rather than timely resolution (Figure 6). Pharmacodynamic modeling of MIF-targeted agents has been proposed to optimize this balance between protective immunity and pathological progression (Grandoni, 2020). This bifunctional behaviour highlights MIF as a central regulator of immune equilibrium, in which precise temporal control determines recovery or disease persistence.

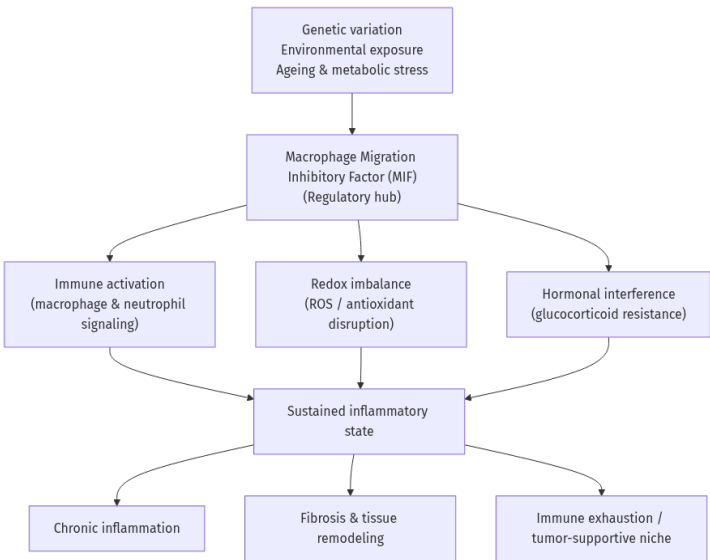


Figure 6: Protective–Pathogenic State-Transition Model of MIF Signaling

5.2 Genetic and Environmental Modifiers

The biological impact of MIF is strongly influenced by genetic variation and environmental exposure. Promoter polymorphisms alter MIF transcriptional activity, modulating susceptibility to inflammatory and autoimmune pulmonary diseases and contributing to inter-individual variability in immune responsiveness. Environmental stressors such as cigarette smoke and airborne pollutants further enhance MIF expression, amplify oxidative stress, and disrupt redox balance. Exosomal transfer of MIF-regulatory microRNAs and proteins between immune and epithelial cells may reinforce these effects by propagating coordinated yet maladaptive signaling across pulmonary compartments (Gurunathan et al., 2021). Together, genetic and environmental factors shape whether MIF-mediated responses remain protective or become pathogenic.

5.3 Dose- and Duration-Dependent Effects

MIF activity is also governed by concentration and exposure duration. Acute, low-level expression supports cytoprotection by stabilizing mitochondrial function, maintaining antioxidant defenses, and enabling controlled immune activation. In contrast, chronic overexpression promotes resistance to apoptosis, fibroblast proliferation, and sustained cytokine release, thereby locking immune responses into a self-perpetuating inflammatory and fibrotic state. Maintenance of physiological redox balance through adequate micronutrient availability may indirectly restrain excessive MIF signaling (Mitra et al., 2022), while antioxidant and anti-inflammatory natural compounds, including *Nigella sativa* derivatives, have been reported to attenuate exaggerated MIF activity and partially restore immune homeostasis (Hannan et al., 2021).

Overall, the functional polarity of MIF reflects the combined influence of genetic predisposition, environmental exposure, redox status, and temporal dynamics of cytokine signaling. Transient activation promotes antimicrobial defense and tissue protection, whereas persistent signaling drives chronic inflammation, oxidative stress, and fibrotic remodeling. Therapeutic strategies must therefore selectively suppress pathogenic MIF activity while preserving its essential roles in host defense and repair (Table 3).

Table 3: Disease-Specific Parameter Shifts in the MIF Network

Disease	Dominant Module	Network Shift	Pathological Outcome
Pneumonia / ARDS	CXCR–NF- κ B	High Gain, Short Duration	Cytokine Storm
COPD	MAPK–MKP-1	Sustained Activation	Steroid Resistance
IPF	ERK–FAK–TGF- β	Fibrotic Bias	Matrix Accumulation
Lung Cancer	PI3K–Immune Suppression	Immune Escape	Tumor Progression

6. Clinical and Translational Perspectives

6.1 MIF as a Biomarker of Disease Activity

Macrophage migration inhibitory factor (MIF) has emerged as a promising biomarker for pulmonary and systemic inflammatory disorders. Persistent elevation of MIF in serum, bronchoalveolar lavage fluid, and exhaled breath condensates has been associated with disease activity and progression in chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and selected malignancies. Rather than reflecting isolated inflammatory events, sustained MIF expression mirrors ongoing dysregulation of immune and redox control mechanisms within the pulmonary system. Chronic inflammatory states involving hepatic and pulmonary dysfunction display altered cytokine signatures in which MIF serves as a predictor of disease severity and systemic involvement (Soulaidopoulos et al., 2020). In addition, circulating extracellular vesicles enriched with MIF-associated proteins have been identified as indicators of immune activation and endothelial dysfunction in lung disease (Mohan et al., 2020). Together, these observations support the utility of MIF as a noninvasive biomarker for capturing disease burden, therapeutic responsiveness, and relapse risk across chronic respiratory conditions.

6.2 Therapeutic Targeting Strategies

Therapeutic modulation of MIF represents an expanding area of translational investigation. Multiple strategies have been developed to inhibit MIF expression or signaling, including small-molecule inhibitors such as ISO-1, 4-IPP, and CPSI-1306, which interfere with MIF tautomerase activity or disrupt receptor engagement. Pharmacological attenuation of MIF-driven inflammasome activation has been shown to restore autophagic processes and reduce proinflammatory cytokine release, thereby rebalancing immune regulatory pathways (Liu & Zhang, 2025). In oncological models, MIF antagonism results in suppression of angiogenic and metastatic signaling, reinforcing its therapeutic relevance across inflammatory and neoplastic pulmonary pathologies (Soumoy et al., 2019).

In parallel, monoclonal antibodies and receptor antagonists targeting CD74 and CXCR4 have demonstrated efficacy in

preclinical respiratory models. Natural bioactive compounds, including green tea polyphenols, have been proposed as adjunctive modulators capable of dampening MIF-mediated inflammation through redox-sensitive mechanisms (Tallei et al., 2021). Collectively, these approaches define a multifaceted therapeutic landscape that integrates synthetic inhibitors, biologics, gene-based interventions, and nutraceutical strategies. The principal categories of MIF-targeted therapies, their mechanisms of action, and current stages of development are summarized in Table 4.

Table 4: Overview of Current Therapeutic Strategies Targeting MIF Signalling in Pulmonary Disorders

Therapeutic Class	Representative Agent(S)	Mechanism of Action	Development Stage	Potential Clinical Application / Supporting Reference
Small-Molecule Inhibitors	ISO-1, 4-IPP, CPSI-1306	Inhibit MIF tautomerase activity and receptor binding through interaction with the catalytic N-terminal proline site.	Preclinical to early clinical	COPD, pulmonary fibrosis, ARDS (Ouertatani-Sakouhi et al., 2010)
Monoclonal Antibodies Receptor Antagonists	Anti-MIF mAb, BaxG03	Neutralise circulating MIF and block CD74/CD44-mediated signalling	Preclinical	Inflammatory lung diseases, oncology (Mizue et al., 2005)
	CXCR4 inhibitors (AMD3100)	Block MIF-CXCR4/CXCR7 interaction, disrupting chemokine-driven inflammation and tumour progression.	Clinical evaluation (repurposed drugs)	Lung cancer, fibrosis (Khezrian et al., 2024)
Gene-Silencing Approaches	siRNA or antisense oligonucleotides	Suppress MIF transcription or translation to reduce cytokine amplification and macrophage activation.	Experimental	Personalised pulmonary therapy (Jalaie et al., 2004)
Natural Compounds	Epigallocatechin gallate, curcumin, thymoquinone	Downregulate MIF via redox modulation and NF-κB suppression pathways	Nutraceutical / preclinical	Adjunct therapy for chronic inflammation (Merecz-Sadowska et al., 2020)
Nanoparticle-Based Delivery	Drug-loaded nanoparticles targeting MIF	Enhance pulmonary delivery and bioavailability of MIF inhibitors; inhibit infection-driven inflammation	Preclinical / translational	ARDS, chronic airway inflammation (Doroudian et al., 2020)
Computational and ADMET Optimization Curcumin Analogs and Bioactives	In-silico screening of MIF inhibitors	Use molecular docking and pharmacokinetic modelling to optimize drug-likeness and safety	In-silico	Preclinical drug design and toxicity prediction (Nagarajan et al., 2024)
	Curcumin derivatives	Exhibit anti-inflammatory and MIF-modulatory activity through computationally validated ADME-toxicology profiles	Preclinical	Potential adjuncts for chronic inflammatory pulmonary diseases (Chabib et al., 2017)

6.3 Challenges and Future Prospects

Despite encouraging progress, several challenges limit the clinical translation of MIF-targeted therapies. A major constraint arises from the structural homology and partial functional redundancy between MIF and D-dopachrome tautomerase (DDT), complicating selective inhibition strategies. Inter-individual variability driven by MIF promoter polymorphisms further influences therapeutic responsiveness and susceptibility to adverse immune modulation. In addition, the interconnected nature of cytokine networks and heterogeneity in interleukin expression patterns introduce complexity in predicting treatment outcomes, underscoring the need for precision-oriented approaches (Al-Qahtani et al., 2024).

Future clinical development programs should therefore integrate pharmacogenomic profiling with longitudinal biomarker monitoring to guide patient stratification and therapeutic optimization. Personalized medicine strategies focused on MIF genotypes, receptor variants, and dynamic immune signatures hold promise for maximizing therapeutic benefit while minimizing systemic immune disruption. Such integrative frameworks align translational MIF targeting with individualized pulmonary care and systems-level disease management.

7. Pharmacokinetic, ADMET, and Delivery Considerations in MIF-Targeted Therapeutics

The clinical translation of macrophage migration inhibitory factor (MIF)-targeted therapeutics requires comprehensive pharmacokinetic (PK) and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) evaluation. Given MIF's involvement in multiple immunoregulatory pathways, indiscriminate inhibition may disrupt the physiological balance of the immune system. Effective dose design therefore depends on integrating molecular disposition with dynamic immune regulation to achieve selective modulation rather than global suppression (Döllner et al., 2002) (Table 5).

Table 5: Systems-Level Variables and Observables in MIF Signaling Relevant to Pulmonary Disease

System Component	Variable Type	Biological Role Within the MIF Network	Measurable Observable	Clinical / Translational Relevance
MIF Expression Level	State Variable	Central driver of immune and redox network activation	Serum MIF, BAL MIF	Disease activity, prognosis, relapse risk
CD74/CD44 Signaling	Regulatory Node	Integration of cytokine signaling with cell survival and proliferation	pERK, pAKT levels	Steroid resistance, chronic inflammation
CXCR2/CXCR4 Signaling	Flux Variable	Chemokine-like control of leukocyte recruitment	Neutrophil counts, chemotaxis assays	Acute inflammation severity
NF- κ B Activity	Feedback Mediator	Amplification of proinflammatory cytokine production	TNF- α , IL-6, IL-1 β	Chronic inflammatory burden
Nrf2 Suppression	Control Variable	Regulation of antioxidant defense and redox balance	ROS markers, antioxidant enzymes	Oxidative lung injury
MKP-1 Inhibition	Switch Element	Persistence of MAPK signaling cascades	p38/ERK activation status	Glucocorticoid refractoriness
Macrophage Polarization	Output State	Balance between proinflammatory and reparative immunity	M1/M2 marker expression	Tissue injury vs repair
Fibroblast Activation	Downstream Outcome	Immune-stromal coupling and matrix deposition	Collagen I, fibronectin	Fibrosis progression
Immune Exhaustion Markers	System Adaptation	Long-term immune dysregulation	PD-1, TIM-3 expression	Chronic disease and ageing

7.1 Absorption and Distribution

Cytokine inhibitors, including MIF-targeted agents, frequently exhibit limited oral bioavailability due to poor aqueous solubility and membrane permeability (Orita et al., 2002). Small-molecule tautomerase inhibitors such as ISO-1 and 4-IPP demonstrate restricted absorption via conventional administration routes (Xu et al., 2013). Pulmonary-targeted delivery approaches, including inhalable formulations and nanoparticle-based carriers, improve lung bioavailability while maintaining localized exposure and minimizing systemic dissemination (Höllriegl et al., 2018). Preclinical pharmacokinetic studies confirm sustained pulmonary tissue concentrations with reduced systemic toxicity (Williams et al., 2007). These observations emphasize the importance of early ADME profiling to guide formulation strategies and predict distribution behavior (Wang & Urban, 2004). Computational approaches predicting tissue penetration, receptor occupancy, and spatial drug distribution further support rational immunomodulator design (Balachandran et al., 2011).

7.2 Metabolism and Biotransformation

MIF inhibitors are primarily metabolized by cytochrome P450 enzymes, notably CYP3A4 and CYP2C9, resulting in relatively short elimination half-lives. Structural optimization strategies, including halogen substitution and steric shielding, have been employed to enhance metabolic stability and prolong systemic exposure (Kallen, 2007). Structure-based drug design combining molecular docking and pharmacophore modeling enables identification of metabolically resilient scaffolds while minimizing reactive metabolite formation (Wang et al., 2018). Computational pharmacokinetic models further simulate hepatic and extrahepatic metabolism to predict clearance before in vivo evaluation (Morris & Lim-Wilby, 2008). Integration of in silico and in vitro metabolism data supports early identification of compounds with favorable exposure profiles and reduced inter-individual variability (Van Montfort & Workman, 2017).

7.3 Structure-Based and AI-Driven Modeling

Crystal structure elucidation of MIF and its complexes with CD74/CD44 has facilitated rational inhibitor design by revealing key binding interactions within the tautomerase active site (Bloom et al., 2016). Molecular docking studies provide insight into binding stability and selectivity across candidate compounds (Swanson et al., 2024). Advances in computational pharmacokinetics enable large-scale parameter prediction across virtual compound libraries, accelerating lead identification (Jayatunga et al., 2022). Machine-learning models, including ADMET-AI platforms, integrate physicochemical, structural, and toxicological descriptors to forecast ADME behavior and prioritize drug-like candidates (Wang & Zhou, 2016). Artificial intelligence-driven screening pipelines increasingly refine compound selection by integrating predicted efficacy, safety, and pharmacokinetic performance (Kumar et al., 2017).

7.4 ADME–Toxicology and Safety Profiling

Toxicological evaluation remains a critical determinant for cytokine-modulating therapies. Excessive suppression of MIF activity may perturb redox signaling, mitochondrial function, and immune resilience (Larbi et al., 2007). Controlled inhibition strategies aim to preserve beneficial immunoregulatory effects while limiting oxidative imbalance and off-target

toxicity (Xiong et al., 2021). Nanoparticle-based delivery platforms enhance safety margins by restricting drug exposure to pulmonary tissue and reducing systemic accumulation (Sączewski et al., 2024). In silico tools such as ADMETlab 2.0 and SwissADME enable early prediction of mutagenicity, hepatotoxicity, and cardiotoxicity during lead optimization (Danhof, 2016; Hopkins, 2008). Coupling these predictions with computational PK/PD modeling further refines therapeutic windows and dose selection (Ursu et al., 2011).

7.5 Systems Pharmacology and Translational Modeling

Systems pharmacology frameworks integrate cytokine network dynamics with PK/PD parameters to predict therapeutic efficacy in complex inflammatory settings. Models incorporating interactions between MIF and downstream immune mediators enable simulation of dose-dependent network responses and identification of optimal intervention points (Cherkasov et al., 2014). Quantitative structure–activity relationship analyses and drug-likeness algorithms further ensure compatibility between chemical properties and biological performance (Skeens et al., 2022; Tripathi et al., 2019). Contemporary in silico ADME workflows link physicochemical attributes with clinical exposure predictions, unifying metabolism, toxicity, and efficacy data into translational models supporting personalized therapeutic strategies (Ancuceanu et al., 2025; Wang et al., 2015).

8. Future Directions

Advancing understanding of macrophage migration inhibitory factor (MIF) as a regulator of pulmonary disease progression highlights the need for integrative strategies that unite molecular, cellular, and computational perspectives. Multi-omics approaches, including single-cell transcriptomics, proteomics, and metabolomics, provide powerful means to resolve the heterogeneity and context dependence of MIF-associated signaling programs within complex lung microenvironments (Selvarajah et al., 2023). High-resolution profiling of immune and stromal cell populations enables identification of MIF-driven regulatory states that remain obscured in bulk analyses, while multi-scale modeling and integrative mapping of cytokine interaction networks can accelerate the discovery of pathogenic MIF-dependent modules and novel therapeutic entry points in fibrotic and inflammatory lung disease (Schuliga et al., 2018). Integration of machine-learning frameworks with large-scale omics datasets further supports prediction of MIF-mediated immune responses, facilitating earlier and more precise intervention. Age-related alterations in immune homeostasis and metabolic regulation add further complexity, as senescent immune cells exhibit elevated MIF expression that sustains low-grade inflammation and disrupts mitochondrial redox balance, reinforcing maladaptive signaling during fibrotic progression under oxidative and metabolic stress (Rajasegaran et al., 2023). Targeted modulation of MIF in this context may restore metabolic flexibility, limit chronic inflammatory amplification, and improve immune surveillance in ageing lung tissue. In parallel, therapeutic repurposing strategies have identified antifibrotic and immunomodulatory agents capable of suppressing MIF-mediated fibroblast activation and extracellular matrix accumulation (Raavi et al., 2025). Combining MIF inhibitors with corticosteroids, antioxidant therapies, or established antifibrotic agents may yield synergistic benefits while minimizing systemic toxicity. Precision pulmonology approaches that integrate patient-specific MIF expression patterns, promoter polymorphisms, and metabolomic signatures offer a rational framework for individualized intervention, enabling alignment of therapeutic strategies with the context-dependent and dualistic behavior of MIF across heterogeneous pulmonary disease phenotypes.

9. Conclusion

Macrophage migration inhibitory factor (MIF) has emerged as a central regulatory mediator in pulmonary immunity, characterised by its complex, context-dependent molecular and cellular functions. Initially characterised as a pro-inflammatory cytokine, MIF is now recognised to exert dual effects: supporting host defence during acute infection and tissue injury, while promoting chronic inflammation, fibrotic remodelling, and tumorigenesis when regulatory control is disrupted. Through coordinated influence on macrophage activation, T-cell differentiation, redox signalling, and epithelial integrity, MIF occupies a pivotal position, linking immune defence mechanisms to metabolic and oxidative regulation in the lung. Accumulating evidence underscores the value of MIF as both a diagnostic and prognostic biomarker, with circulating and tissue-associated levels correlating with disease activity and progression in chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and lung cancer. Parallel advances in therapeutic development, including small-molecule inhibitors, monoclonal antibodies, and receptor-directed antagonists targeting MIF or its homolog D-dopachrome tautomerase, have expanded opportunities for pharmacological intervention. Nonetheless, challenges related to target selectivity, potential systemic immune suppression, and inter-individual genetic variability continue to complicate clinical translation. Future progress in MIF-directed pulmonary medicine will depend on integrative strategies that combine omics-based profiling, systems pharmacology, and precision-guided clinical approaches. Clarifying the contextual determinants governing whether MIF activity remains protective or shifts toward pathogenic signalling will be essential for selectively

harnessing its beneficial functions while limiting detrimental effects. Deeper insight into the regulatory architecture of MIF-mediated immune responses has the potential to reshape therapeutic paradigms in pulmonary disease, positioning this cytokine as a cornerstone of individualised, mechanism-informed respiratory care.

10. References

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