

## CALL FOR PAPERS | *Biomarkers in Lung Diseases: from Pathogenesis to Prediction to New Therapies*

### Role of macrophage migration inhibitory factor in age-related lung disease

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**Sauler M, Bucala R, Lee PJ.** Role of macrophage migration inhibitory factor in age-related lung disease. *Am J Physiol Lung Cell Mol Physiol* 309: L1–L10, 2015. First published May 8, 2015; doi:10.1152/ajplung.00339.2014.—The prevalence of many common respiratory disorders, including pneumonia, chronic obstructive lung disease, pulmonary fibrosis, and lung cancer, increases with age. Little is known of the host factors that may predispose individuals to such diseases. Macrophage migration inhibitory factor (MIF) is a potent upstream regulator of the immune system. MIF is encoded by variant alleles that occur commonly in the population. In addition to its role as a proinflammatory cytokine, a growing body of literature demonstrates that MIF influences diverse molecular processes important for the maintenance of cellular homeostasis and may influence the incidence or clinical manifestations of a variety of chronic lung diseases. This review highlights the biological properties of MIF and its implication in age-related lung disease.

MIF; lung; innate immunity

THE LUNGS ARE VULNERABLE TO age and age-related diseases. Aging reduces ventilatory capacity and increases vulnerability to environmental stressors, including inhaled substances and microorganisms. Respiratory infections, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), lung cancer, and interstitial lung disease all increase in prevalence with age. Because the number of Americans over age 65 is estimated to almost double within the next 20 years, there is an urgency to understand the fundamental biological mechanisms that predispose the aged lung to disease (140, 145).

With age, the capacity of cellular stress responses to maintain homeostasis in the face of environmental toxins, pathogens, and dysregulated intrinsic cellular processes is impaired (56). Perhaps nowhere is this age-related impairment more important than in the lung, which represents the largest interface between the internal and external environments. Here alveoli are continuously exposed to aerosolized pollutants, infectious agents, and oxidants (140). Both innate and adaptive immune responses are among the cellular stress responses that are compromised with age. Advanced age is associated with decreased neutrophil function, attenuated innate immune signaling, and a decreased repertoire of adaptive immune responses (39, 101, 127, 128). This aging immune response has been implicated in the increased prevalence of respiratory infec-

tions among the elderly. Yet, beyond its antimicrobial responses, the immune system is critical for sensing changes in the alveolar microenvironment and integrating with diverse cellular signaling pathways to maintain tissue homeostasis, which is critical for optimal respiratory function (28, 66, 70, 89, 102, 159, 161). The noninfectious consequences of age-related changes in immune function are only beginning to be understood.

Macrophage migration inhibitory factor (MIF) is a critical upstream regulator of the immune response (25). MIF induces the expression of cytokines and other inflammatory mediators including TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-2, IL-6, IL-8, IL-12, nitric oxide, specific matrix metalloproteases, and products of the arachidonic acid cascade (25). MIF also upregulates the canonical innate immune receptor Toll-like receptor 4 and specialized microbial sensors such as dectin-1 (33, 120). Highlighting the role of MIF in inflammation, diverse studies have shown that inhibition of MIF can mitigate deleterious inflammation in conditions such as ARDS, asthma, sepsis, and autoimmunity (8, 38, 86, 120, 146). In addition to its immunological function, MIF promotes cellular survival, antioxidant signaling, angiogenesis, and wound repair while mitigating cellular senescence (2, 4, 21, 29, 42, 47, 57, 80, 82, 87, 99, 100, 123, 160). This review will highlight the role of MIF in the pathogenesis of respiratory diseases that disproportionately afflict the elderly.

#### *MIF: Structure and Function*

MIF was first described and named in the 1950s as a lymphocyte-secreted molecule that arrested the migration of macrophages (37). Despite its historical namesake, MIF influ-

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ences numerous cell lineages beyond the myeloid system and is ubiquitously expressed in the airway, alveolar, and resident immune cells of the lung. There is a single human *MIF* gene on chromosome 22 (22q11.23) and both the *MIF* primary sequence and three-dimensional structure are evolutionarily conserved (31, 77, 108, 135). The gene lies in close proximity to two theta-class glutathione *S*-transferases and D-dopachrome tautomerase (D-DT) (18, 91, 92, 114). D-DT is structurally homologous to MIF and shares many of its biological functions. Two polymorphisms in the promoter region of the *MIF* gene are commonly associated with disease. The first is a microsatellite repeat:  $-794 \text{ CATT}_{5-8}$  (*rs5844572*), in which the number of CATT repeats directly regulates *MIF* expression. The second is a  $-173 \text{ G/C}$  single nucleotide polymorphism (SNP) (*rs755622*) in which the C allele is in linkage disequilibrium with the high-expression  $-794 \text{ CATT}_7$  allele. The functional  $-794 \text{ CATT}_{5-8}$  microsatellite structural variant is not represented in the SNP-based chips used for genomewide association studies, and its impact on genetic susceptibility has only been uncovered by candidate gene studies. To date, *MIF* alleles and their haplotypes have been implicated in the incidence or clinical severity of various infectious and autoimmune diseases, as well as immune-related disorders such as autism, or cancers in which inflammation is considered to promote tumor growth (11, 20, 53, 98).

MIF exists preformed in cytoplasmic pools and is rapidly secreted in response to diverse stimuli including oxidative stress and bacterial products (16, 136). The MIF translation product lacks a  $\text{NH}_2$ -terminal sequence for translocation into the endoplasmic reticulum, similar to other nonclassical secretory proteins, such as IL-1 $\beta$  or FGF-1 (48). In macrophages, a specialized pathway for MIF export exists that requires MIF interaction with the Golgi-associated protein, p115 (90). MIF secretion is markedly reduced following treatment with glyburide and probenacid, implicating the involvement of the ABCA1 transporter in MIF secretion (48). In the pituitary, MIF is secreted along with ACTH in response to stress (7, 149). Physiological concentrations of glucocorticoid regulate MIF secretion, and circulating MIF demonstrates a similar diurnal rhythm as glucocorticoids (23, 45, 110). Interestingly, MIF can override the effects of glucocorticoids via diverse signaling pathways that include 1) inhibition of glucocorticoid induction of I $\kappa$ B $\alpha$  (36), 2) inhibition of glucocorticoid-mediated transcription of MAP kinase phosphatase-1 (4, 117), and 3) autocrine and/or paracrine activation of a proinflammatory signaling cascade via binding to its receptor, CD74 (74) (Fig. 1).

CD74 is the cell surface expressed form of the MHC class II-invariant chain. It was initially described to play an important role in peptide loading onto MHC class II molecules. However, in 2003, Leng et al. (74) described CD74 to be the cell surface receptor for the MIF molecule. High-affinity binding of MIF to the CD74 ectodomain relies on structural features of MIF's vestigial tautomerase (44). In a healthy lung, CD74 has been described on macrophages and type II pneumocytes, but upon activation CD74 is upregulated in both epithelial and endothelial cells (14, 85, 124, 132). The intracellular domain of CD74 is phosphorylated upon MIF engagement, but it lacks canonical signaling motifs and recruits its coreceptor CD44 to initiate a Src kinase-dependent signaling cascade (129). Different downstream signaling pathways have been demonstrated in different cell types. MIF induces ERK1/2

and PI3K-AKT signaling and results in NF- $\kappa$ B-mediated transcription and activation of the arachidonic acid cascade. In addition to mediating MIF's involvement in host immunity and inflammation, these pathways are also implicated in MIF's role in cell survival and angiogenesis (79, 80, 93).

MIF promotes cellular growth and survival via multiple pathways. Critical to MIF's function is its central ability to protect cells from activation-induced apoptosis (24, 38, 47, 99, 120). The mechanism by which MIF suppresses p53 activation has been described to occur via multiple pathways. These include direct protein-protein interactions and CD74-mediated AKT activation (64, 65, 80). MIF has also been shown to mitigate p53-mediated apoptosis via its binding to c-Jun activation domain-binding protein-1 (JAB1) to modulate AP-1-mediated transcription factors (68, 104). JAB1 is a key component of the COP9 signalosome and the MIF-JAB1 interaction has been implicated in the regulation of integrins, cell-cycle regulatory proteins, and apoptosis (79, 103, 107). MIF can activate other signaling pathways that have been implicated in cell survival. Treatment of cardiomyocytes with exogenous MIF results in the phosphorylation of AMPK in a CD74-dependent manner (95). Paradoxically, MIF is a negative regulator of the AMPK signaling pathway in transformed human non-small cell lung cancer cell lines (19). Similarly, MIF mediates JNK and NO signaling pathways in a context-dependent manner (78, 113). In B cells, MIF initiates a specialized pathway of regulated intramembranous cleavage of CD74 to generate an intracytoplasmic CD74 peptide that activates RelA-dependent transcription (131).

There are other consequences of MIF signaling that are likely important in respiratory biology. MIF inhibits the expression of cellular senescence genes (106, 152). Cellular senescence is a hallmark of aging and is characterized by cell cycle arrest, either from repetitive cell division or from accumulated damage from oxidative stress (27, 116). Cellular senescence occurs in aging-related lung disease such as idiopathic pulmonary fibrosis, lung cancer, and COPD (22, 97). MIF inhibits the expression of cyclin-dependent kinase inhibitors including p21 and p16 (84, 106, 109, 123, 152). The pathological manifestations and clinical consequences of MIF's role in cellular senescence have not been thoroughly defined. MIF also has an important role in angiogenesis. Hypoxia is a potent inducer of angiogenesis via activation of hypoxia inducible factor (HIF-1) family of transcription factors. MIF and vascular endothelial growth factor (VEGF) are among its many target genes that promote angiogenesis via binding to their HIF1 promoter binding sites (12, 137). Reciprocally, MIF can help stabilize HIF-1 $\alpha$  and enhance its transcription (55, 82, 155). MIF chemotactic function has been implicated in atherosclerotic plaque formation and the recruitment of cells important for neovascularization, such as endothelial progenitor cells (54, 75, 125, 130). Finally, MIF functions as a chemotactant for neutrophils, monocytes/macrophages, and lymphocytes to sites of injury. Although MIF does not possess the  $\text{NH}_2$ -terminal cysteine motif of classically defined chemokines, it does possess a *pseudo-(E)LR* motif (Asp44-X-Arg11) that imparts its chemokine-like function by activation of the receptors CXCR2 and CXCR4 (17). These receptors can form heteromeric complexes with CD74. Notably, the other member of the MIF superfamily, D-DT, lacks this domain and has an attenuated ability to recruit neutrophils (69, 151).

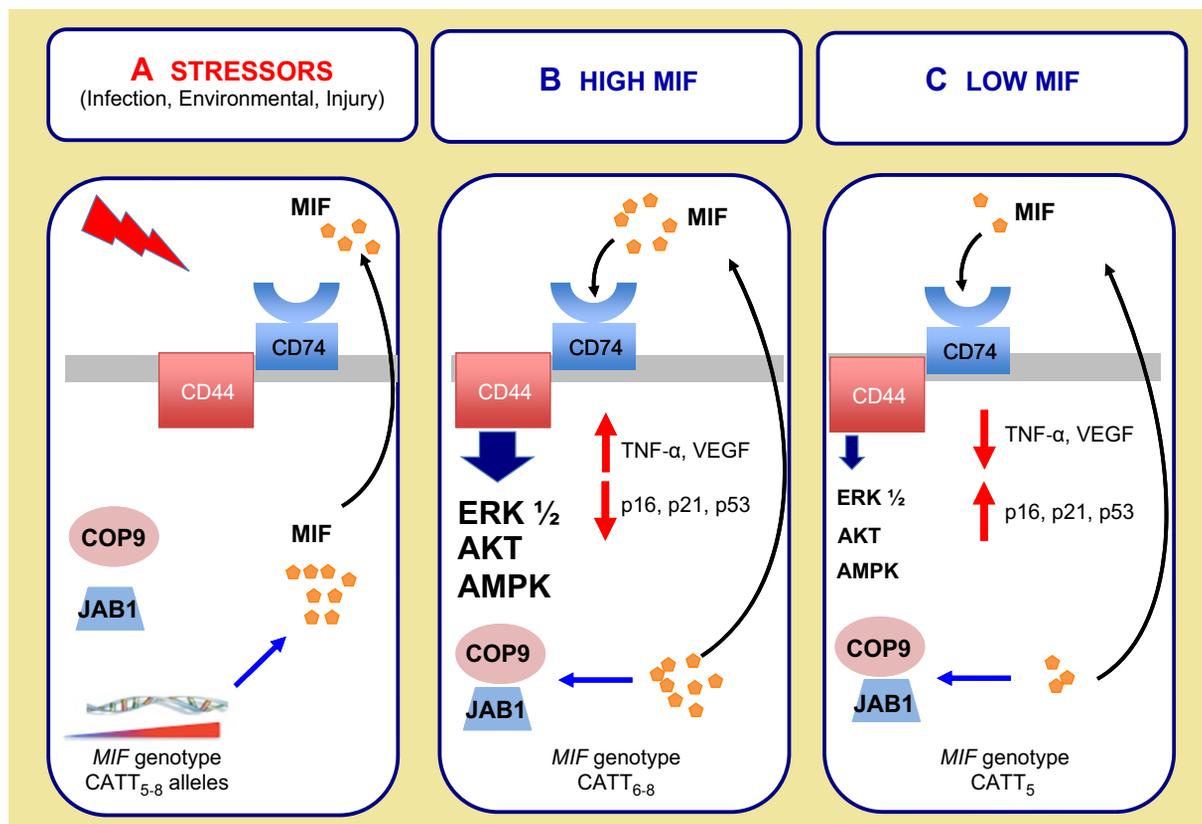


Fig. 1. *A*: in response to diverse biological stressors, macrophage migration inhibitory factor (MIF) is secreted from preformed intracytoplasmic pools. Subsequently there is an increase in MIF gene transcription. A CATT microsatellite repeat in the promoter region influences gene transcription. *B*: MIF can signal through its receptor CD74 and coreceptor CD44 to activate ERK 1/2, AKT and AMPK signaling pathways or via an intracellular JAB1 pathway. High MIF conditions result in the transcription of proinflammatory and angiogenic mediators such as TNF- $\alpha$  and VEGF. MIF is also a key cell cycle regulator and can suppress p53- and p16-mediated apoptosis and/or cellular senescence. High-expressing CATT<sub>6-8</sub> alleles correspond to increased MIF gene expression. *C*: the CATT<sub>5</sub> allele is associated with decreased transcription of MIF. Low MIF states result in relatively decreased transcription of proinflammatory and angiogenic mediators and a relatively increased susceptibility to apoptosis and cellular senescence.

#### MIF in Animal Models and Human Studies of Age-Related Lung Disease

**MIF in respiratory infection, sepsis, and ARDS.** Respiratory infections are a leading cause of death in the elderly. Individuals older than 65 demonstrate an increased incidence of pneumonia compared with younger adults, and the highest incidence of pneumonia is among individuals >80 years of age (50). MIF is an important component of the antimicrobial response to infection. MIF is secreted into the alveolar space as a consequence of diverse pathological microorganisms and mediates inflammation and host defense. In certain contexts, this response may be maladaptive. Increased MIF is associated with increased pathogenicity of *Pseudomonas pneumoniae*, a phenomenon that is supported by genetic studies in patients with cystic fibrosis (3). Similarly, MIF is increased in patients with *Burkholderia pseudomallei* and neutralization of MIF improves bacterial clearance of this pathogen in animal models of this disease (154). In sepsis, a systemic consequence of severe infection, intracellular MIF is significantly increased in immune cells and circulating concentrations of MIF correlate with clinical severity (7, 16, 26, 41). Similar associations have been demonstrated in ARDS (38, 51, 72). *Mif*-knockout mice or mice treated with systemic MIF inhibitors are protected against lethal doses of LPS or gram-positive exotoxins. Neu-

tralization of MIF or *Mif* deficiency is associated with improved outcomes in multiple murine models of sepsis (26, 49, 118, 121).

However, the role of MIF in respiratory infection and sepsis is context dependent. Genetic variations consistent with low *MIF* expression are associated with increased risk for community-acquired pneumonia and recent studies have demonstrated that *Mif*-knockout mice have increased *Streptococcus pneumoniae* nasal carriage and decreased clearance of these bacteria (34, 158). MIF is critical for the transcription of the pattern recognition receptor dectin-1, which is important for mediating clearance of *Mycobacterium tuberculosis* (33). *Mif* knockout mice have impaired killing of gram-negative bacteria by macrophages and increased susceptibility to *Klebsiella pneumoniae* (119). Similarly, there was significant enrichment of the low-expressing *MIF* allele among older individuals with gram-negative sepsis compared with healthy controls (35). It also has been shown that *Mif*-knockout mice have an impaired ability to clear secondary bacterial infections (111), and in a hyperoxic murine model of acute lung injury, both *Mif*- and *Cd74*-knockout mice have increased disease severity (124). Ultimately, MIF secretion in response to infection may have pathogenic consequences of overwhelming cytokine release and inflammation, but it likely plays an important role in

routine clearance of potentially pathogenic organisms that are frequently involved in pneumonia in the elderly.

**MIF and chronic obstructive pulmonary disease.** COPD is the third leading cause of death in the United States and occurs predominately among individuals greater than 45 years of age (112, 140). COPD is associated with an increase in cellular senescence, DNA damage, and oxidative stress (5, 144, 157, 161). Four studies have now evaluated circulating concentrations of MIF in COPD and have produced substantially similar findings, albeit with some nuanced differences. One study demonstrated that those with very severe disease, when compared with “never smokers,” had decreased levels of circulating MIF (42). Another study comparing never smokers, smokers without COPD, and smokers with COPD demonstrated that whereas plasma MIF was increased in “healthy” smokers compared with never smokers, plasma MIF was decreased in those with COPD compared with smokers without COPD (123). A third study suggested that peripheral blood mononuclear gene expression of MIF inversely correlated with disease severity as measured by percent emphysema and spirometric evidence of airway obstruction (9). Finally, a recent study, and the largest of its kind, has shown that, although MIF was increased in moderate disease (GOLD II) compared with healthy never, current, and former smokers, there was a significant decrease in circulating MIF among patients with severe and very severe disease (GOLD III, IV) (61). Overall these studies suggest that although MIF may be increased among healthy smokers or smokers with moderate disease, circulating levels of MIF fall as the disease progresses. Interestingly, such findings have been recapitulated in experimental animal models. Although 3 mo of cigarette smoke exposure in mice led to increased concentrations of MIF in the bronchoalveolar lavage (BAL) fluid, 6 mo of exposure, a time course consistent with the development of COPD in animal models, resulted in a decrease in total protein and BAL concentrations of MIF (123).

Histone deacetylase 2 (HDAC-2) function is diminished in COPD and potentially may account for decreased *MIF* gene expression in this disease (62, 81). *Mif*- and *Cd74*-knockout mice both develop spontaneous emphysema (123). Similarly, *Mif*-knockout mice demonstrate increased air space enlargement and apoptosis following exposure to chronic cigarette smoke (32, 42, 123). There are multiple MIF-related signaling factors that may contribute to this phenomenon. MIF may promote lung activation of NRF-2, which is a critical antioxidant transcription factor that is decreased in the lungs with age and in COPD (87). Since oxidative stress is a critical mediator of COPD, the blunting of antioxidants as a consequence of MIF deficiency may accelerate the progression of COPD. The BAL of *Mif*-knockout mice demonstrate increased markers of oxidative stress with age. Additionally, both the p16-RB and p53-21 cellular senescence pathways are suppressed by MIF and the lungs of *Mif*-knockout mice demonstrate increased markers of both cell senescence pathways with age (123). As cellular senescence is associated with the secretion of proinflammatory cytokines, this cellular senescence associated phenotype may contribute to ongoing inflammation and air space enlargement in the lungs of patients with COPD (59, 71, 143, 144, 148). Finally, diminished VEGF and vasculogenesis have been implicated in the pathogenesis of COPD (138, 147), and *Mif*-knockout mice show decreased VEGF signaling in the lung in response to oxidative stress (134).

It should be noted that an opposite relationship exists between *MIF* expression and clinical outcomes in asthma. In asthma, a low-expressing *MIF* genotype is associated with milder disease. Similarly, in the ovalbumin model of asthma, *Mif*-knockout mice show decreased airway hyperresponsiveness compared with control mice (100, 122). Because there is an overlap between COPD and asthma, it is interesting to consider the possibility that elevated *MIF* expression contributes to a certain proinflammatory airway subtype of COPD whereas decreased *MIF* expression contributes to cellular senescence, apoptosis, and vascular attrition, which are all considered to be part of the pathology of COPD.

**MIF and non-small cell lung cancer.** Similar to other chronic respiratory diseases, the incidence of lung cancer increases with age. MIF's biological activity may contribute to the inflammatory pathogenesis of cancers by multiple mechanisms. MIF induces sustained ERK1/2 activation, which mimics oncogenic mutations in *Ras*, contributes to tumor growth and invasiveness, and upregulates VEGF leading to neovascularization. MIF can simulate mutations in two important tumor suppressors by suppressing p53-mediated growth arrest and apoptosis and disrupting the Rb-E2F signaling pathway (21, 30, 60, 99, 109). MIF also can inhibit T cell cytolytic responses (1). There is increased immunohistochemical staining of MIF and CD74 in most patients with non-small cell lung cancer, and MIF may even represent an early biomarker of disease (76, 88). Increased circulating MIF is associated with poorer outcomes and with increased circulating levels of angiocrine factors (67, 141, 153). No associations between *MIF* genotypes and lung malignancy have been reported to date, but in other cancers high-expressing *MIF* polymorphisms have been linked with incidence and/or invasiveness of disease (43, 94). Longevity studies in *Mif*-knockout mice demonstrated a marked increase in malignancies (with the notable exception of a marked decrease of hemangiosarcomas). These studies, together with data from experimental tumor models, suggest that anti-MIF therapy may be beneficial for the treatment of malignancies, and cancer is the first clinical indication for which humanized anti-MIF and anti-CD74 are being evaluated (52). However, critical unanswered questions remain. Does MIF contribute to a tumor-permissive microenvironment that allows the growth and replication of precancerous cells or does MIF's biological activity contribute to de novo mutations in the cellular genome? Investigations into these pathways suggest that MIF's role in the cell cycle is complex. A study comparing spontaneous mutations in *p53*-null mice with *p53/Mif* double-knockout mice demonstrated a shift in the spectrum of tumors with the single mutation *p53*-null mice demonstrating a decrease in T cell tumors but an increase in B cell lymphomas, hemangiosarcomas, and carcinomas compared with the double-knockout mice (103). MIF has been demonstrated to regulate cyclin-dependent kinases and E2F transcription binding via both JAB-1 and CD74 pathways that promote transition through various stages of the cell cycle and cell growth (46). In addition to being critical regulators of the cell cycle, cyclin-dependent kinases and E2F transcription factors play an important role in the DNA damage responses and can promote DNA repair in response to injury. Interestingly, we and others have identified increased markers of DNA damage in *Mif*-knockout mice suggestive of defective DNA repair (42, 124). This complex relationship

between immune function, cell cycle regulation, DNA repair, and cancer requires further investigation.

**MIF and lung fibrosis.** Lung fibrosis is associated with numerous hallmarks of aging including telomere shortening, oxidative stress, and aberrant extracellular matrix deposition (73). MIF is increased in the BAL of patients with idiopathic pulmonary fibrosis (IPF) (10, 83). Immunohistochemical analysis of lung tissue of patients with IPF demonstrated increased MIF in the epithelium and fibroblastic foci. The measurement of MIF in the BAL of mice following treatment with the fibrogenic agent bleomycin similarly demonstrated an increase in *Mif* expression. In one murine study, although treatment with anti-MIF antibody mitigated the acute effects of bleomycin-induced lung injury, there was no difference in hydroxyproline content or histopathological lung fibrosis scoring (139). Radiation-induced lung injury can often lead to pulmonary fibrosis in patients being treated for cancer (87). Aged, but not young, *Mif*-knockout mice appear to be sensitive to radiation-induced lung injury (87). This finding correlated with decreased antioxidant production in these *Mif*-knockout mice. A recent study has demonstrated that *Mif*-knockout mice were protected against hepatic fibrosis in multiple models of chronic liver injury and suggested the importance of MIF-CD74-AMPK signaling in mitigating PDGF activation of hepatic stellate cells (58). These data collectively suggest that the MIF signaling axis may be important in lung fibrosis, but further work is necessary to determine the exact role of MIF in the pathogenesis of fibrotic lung disease.

#### MIF and Longevity

Growing evidence suggests a role for MIF in aging and age-related lung diseases. In multiple aging rodent models, MIF secretion diminishes with age, including the lung (87, 123). Simultaneously, MIF was shown to be elevated in certain long-lived mouse breeds and following caloric restriction (96). Human studies have not shown a decline in MIF with age. However, in the setting of sepsis, individuals older than 65 with the low-expressing -794 CATT<sub>5</sub> allele demonstrate diminished secretion of MIF (35). One study suggested that *Mif*-knockout mice live longer than control mice. This association persisted in calorically restricted mice as well (57). With the caveat that this study was performed in mice of mixed genetic backgrounds, it highlights the complex nature and important interaction between MIF and aging biology. Recent in vitro studies have also highlighted MIF's role in the modulation of glucose and fat metabolism, mitochondrial respiration, stem cell survival, ubiquitin-proteasome signaling, redox balance, cell cycle regulation, autophagy, and cellular senescence (13, 40, 46, 105, 115, 142, 156).

#### Therapeutic Opportunities

Beyond supportive observations in experimental models of disease, accruing data from human studies suggest a therapeutic rationale for a MIF-based treatment approach to age-related lung diseases. Pharmacological development in this area is advancing and has been facilitated by unique features of the MIF-CD74 interaction (126) and the recent discovery, using structure-based molecular design, of not only MIF antagonists but small molecule agonists that act to increase MIF's affinity and activation of CD74 (63). Whereas MIF antagonists may be

utilized for those indications where excessive MIF production is a clinical feature, small molecule agonists may offer utility in chronic or age-related MIF deficiency (150). Ultimately, such therapies could provide precision-based medical ap-

Table 1. Findings from both human studies and animal models of age-related lung disease

	Human Studies	Animal Studies
Pneumonia	Low-expressing <i>MIF</i> allele is associated with increased mortality from CAP (158)	Anti-MIF antibody reduces cytokine production and increases survival in a mouse model of <i>S. pneumoniae</i> -induced pneumonia (25)
	Low-expressing <i>MIF</i> allele is associated with decreased <i>Pseudomonas</i> colonization and milder disease in cystic fibrosis (3)	MIF promotes clearance of pneumococcal colonization (34)
Acute respiratory distress syndrome	MIF is increased in the blood and BAL of ARDS and is associated with outcome (15, 38)	<i>Mif</i> -knockout mice are protected from ARDS/severe sepsis in various models including LPS, TSST, and <i>Escherichia coli</i> infection (7, 16, 26, 41, 72)
	<i>MIF</i> expression is increased in endothelial cells and macrophages of patients with ARDS (72)	
	MIF neutralizations decreases TNF and IL-8 secretion in cultured alveolar macrophages from patients with ARDS (38)	<i>Mif</i> -knockout mice are susceptible to hyperoxic lung injury (124, 133, 134)
Chronic obstructive lung disease	Polymorphisms in the MIF gene are associated with outcomes in ARDS (51)	
	MIF is increased in healthy smokers OR in moderate COPD (GOLD stage II) compared to control (61, 123)	<i>Mif</i> -knockout and <i>Cd74</i> -knockout mice are susceptible to cigarette smoke and the development of spontaneous emphysema (42, 123)
	PBMC gene expression of <i>MIF</i> is directly associated with FEV <sub>1</sub> percent predicted (9)	MIF is increased in the BAL of mice following short-term cigarette smoke (123)
Non-small cell lung cancer	MIF is decreased in patients with severe COPD (GOLD III/IV) compared to milder disease (42, 61, 123)	MIF is decreased in the BAL and tissue of mice following long-term cigarette smoke (42, 123)
	MIF and CD74 are increased in NSCL cancer tissue compared to normal lung tissue (76, 88)	MIF promotes tumor cell growth in the context of lung injury (6)
Idiopathic pulmonary fibrosis	MIF is associated with vessel density and risk of reoccurrence in lung cancer (67, 141, 153)	
	MIF is increased in the BAL of patients with IPF (10, 83)	Aged <i>Mif</i> -knockout mice are susceptible to radiation-induced lung injury (87)
	MIF is increased in epithelial cells and fibroblastic foci of patients with IPF (10)	

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; COPD, chronic obstructive lung disease; FEV<sub>1</sub>, forced expiratory volume in 1 s; GOLD, Global Initiative for Obstructive Lung Disease; IL-8, interleukin-8; IPF, idiopathic pulmonary fibrosis; MIF, macrophage migration inhibitory factor; PBMC, peripheral blood mononuclear cells; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

proaches to age-related lung diseases in which genetic or acquired deficiencies in *MIF* expression are a pathogenic feature.

### Conclusion

The involvement of MIF in the pathobiology of diverse age-related lung diseases suggests an important role for this protein in the maintenance of respiratory homeostasis. As summarized in Table 1, both human studies and animal models implicate MIF as a fundamental response to disease. Future studies will need to address which in vitro and murine models are the most relevant for human diseases and whether manipulation of the MIF signaling axis can be used as a therapeutic modality. The study of MIF also highlights the complex interaction between innate immunity and age-related lung biology. On one hand, homeostatic *MIF* expression promotes pathogenic clearance, antioxidant signaling, and DNA repair in the lung. However, excess MIF contributes to dysregulated inflammation in syndromes such as ARDS and sepsis. Furthermore, MIF may promote cellular growth, wound healing, and DNA repair at the cost of promoting cellular replication in cells with tumor potential. These complex tradeoffs may underscore the complexity of aging biology. Determining the role of innate immunity in age-related disease may help unravel subtypes of lung diseases that are in need of further refinement, such as COPD; this may lead to new and more precision-oriented approaches to disease prevention and therapy. As we acquire a closer understanding of the immunological changes that occur with aging, fundamental insights into the increased susceptibility of the elderly to lung disease and new opportunities for therapy will ensue.

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### DISCLOSURES

R. Bucala is listed as coinventor on a Yale University patent application describing the potential utility of MIF agonists and antagonists.

### AUTHOR CONTRIBUTIONS

M.S. and P.J.L. conception and design of research; M.S. drafted manuscript; M.S., R.B., and P.J.L. edited and revised manuscript; M.S., R.B., and P.J.L. approved final version of manuscript.

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