MIF and Pulmonary Disease

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Abstract As the organ responsible for gas exchange, the lung represents the largest interface between the external and internal environments. Most of the lung's surface area is a delicate lattice of epithelial-endothelial interfaces that permit the efficient exchange of oxygen and carbon dioxide. To maintain its integrity, the lung requires a complex network of defenses against external toxins and pathogens. Macrophage migration inhibitory factor (MIF) is a multifunctional cytokine that serves as a critical regulator of the innate immune response and mediates protection from oxidative stress in the lung. Both pathologic and protective roles for MIF in lung disease have been described. This chapter will focus on the role of MIF in the pathogenesis of pulmonary disease.

1 MIF, Pneumonia, and Acute Respiratory Distress Syndrome

MIF is secreted into the alveolar space as part of the antimicrobial response to infection. MIF is a critical mediator of host defense and inflammation; however, MIF can be maladaptive when infections lead to excessive inflammation and overwhelming lung injury.

Numerous murine models and clinical studies have demonstrated a protective role for MIF in the context of pneumonia. *Mif*-knockout mice show decreased clearance of *Streptococcus pneumoniae* colonization, increased vulnerability to *Klebsiella*

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pneumoniae, impaired killing of gram-negative bacteria by macrophages, and an impaired ability to clear secondary bacterial infections [1–3]. Additionally, MIF is responsible for the transcription of the pattern recognition receptor, dectin-1, which mediates the clearance of *Mycobacterium tuberculosis* [4]. Human *MIF* alleles associated with decreased MIF expression have been associated with increased susceptibility to community-acquired pneumonia [5]. Similarly, there was significant enrichment of the low-expressing *MIF* allele among older individuals with gram-negative sepsis compared with healthy controls [6]. In these conditions, MIF is important for the clearance of infectious agents associated with pneumonia.

However, under other conditions or in the setting of infection by specific organisms, MIF has been demonstrated to be deleterious. *Mif*-knockout and MIF-inhibited mice show lower levels of inflammation and improved survival against lethal doses of LPS and gram-positive enterotoxins [7, 8]. Similarly, MIF elevation is associated with pathogenicity of *Pseudomonas* pneumonia, and patients infected with *Burkholderia pseudomallei* show increased MIF expression [9]. Furthermore, neutralization of MIF in animal models improves bacterial clearance of *Burkholderia pseudomallei* [10]. In general, neutralization of MIF or *Mif*-knockout has been shown to improve outcomes in murine models of sepsis [11, 12].

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by widespread inflammation of the lungs. ARDS commonly occurs as a consequence of pneumonia or non-pulmonary infections that are complicated by systemic involvement. ARDS has an associated mortality of 25–30%, and currently, the only treatment for this disease is mechanical ventilation and supportive care [13].

MIF is elevated in the plasma, immune cells, and endothelial cells of patients with ARDS, and circulating MIF levels correlate with clinical severity [14–16]. A role for MIF and its receptor CD74 in acute lung injury (ALI) has been suggested by numerous studies that correlate decreased MIF activity with attenuated neutrophil migration and thus increased protection from damage-induced lung inflammation. In a study that used ex vivo human macrophages from ARDS-affected patients, MIF was demonstrated to mediate injurious inflammation and override glucocorticoid anti-inflammatory activity. In this same study, neutralizing MIF attenuates pro-inflammatory cytokine production, illustrating the potential for therapeutic use of anti-MIF therapy in ARDS [17].

In animal models, attenuating MIF activity results in a decreased pulmonary inflammatory response and less severe organ injury [7, 8, 11, 12]. The use of anti-MIF and anti-CD74 antibodies in such studies decreased neutrophil migration in lipopolysaccharide (LPS)-induced ALI [18–20]. Similar findings have been reported in ventilator-induced ALI models and ARDS induced by gram-positive exotoxins [20–22]. As an alternative to anti-MIF antibodies, heme oxygenase-1 expression by administration of cobalt protoporphyrins has been shown to negatively regulate lung MIF and TLR4-induced inflammation in response to LPS [23].

Conversely, MIF has been demonstrated to have a protective effect in certain sterile injury models. Hyperoxia (exposure to 100% oxygen) is a commonly used ALI model in which *Mif*-knockout and *Cd74*-knockout mice demonstrate increased sensitivity to hyperoxia-induced lung injury and decreased median survival relative to WT mice [24]. In neonatal mice, exposure to hyperoxia causes

bronchopulmonary dysplasia (BPD), and *Mif*-knockout^{-} and *Cd74*-knockout pups are similarly susceptible to hyperoxia-induced BPD [25, 26]. BPD is a respiratory disorder that occurs in premature neonates in which prolonged delivery of supplemental oxygen causes alveolar septal injury. Genetic studies have associated low-expression *MIF* alleles with increased susceptibility to BPD. Finally, older $Mif^{-/-}$ mice demonstrate increased susceptibility to radiation-induced lung injury, an effect attributed to the lack of MIF-mediated NRF-2 activation? MIF upregulation of nuclear factor erythroid 2-related factor 2 (NRF-2) in murine endothelial cells [27].

2 MIF and Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is the narrowing and thickening of blood vessels, involving proliferation of lung vascular endothelial and smooth muscle cells, that ultimately leads to hypoxemia and right ventricular failure. Circulating MIF is elevated in patients with idiopathic and scleroderma-associated PAH [28, 29]. In rodent models of PAH, MIF was shown to promote the proliferation of pulmonary arterial smooth muscle cells and activate anti-apoptotic and pro-inflammatory signaling in pulmonary endothelial cells in a CD74-dependent manner. Inhibition of MIF-CD74 interaction using ISO-1, in multiple rodent models, resulted in decreased pulmonary vascular remodeling, cardiac hypertrophy, and right ventricular systolic pressure [6, 28, 30]. These results indicate a potential therapeutic effect of MIF inhibition for patients suffering from PAH.

3 MIF and Chronic Pulmonary Inflammatory Disease

3.1 Chronic Obstructive Pulmonary Disease

COPD is the third leading cause of death in the United States. Emphysema, a hallmark pathologic finding in COPD, is characterized by an imbalance of lung tissue injury and repair. Emphysema is associated with an increase in cellular senescence, oxidative stress, and DNA damage [31–34].

Several studies evaluating circulating MIF in relation to COPD disease severity have revealed similar trends in MIF concentration and disease pathogenesis. The cumulative data from three studies suggest that MIF is significantly increased in "healthy" smokers or smokers with mild disease. However, in severe disease, circulating MIF concentrations are diminished [35, 36]. These findings have been recapitulated in experimental animal models where mice exposed to cigarette smoke for 3 months exhibited increased MIF concentration in bronchoalveolar lavage (BAL), but at 6 months of exposure—a time course consistent with COPD development in mice—BAL and circulating MIF concentration were decreased [35–38]. Both *Mif*-knockout and *Cd74*-knockout mice spontaneously develop airspace enlargement, and *Mif*-knockout mice are prone to cigarette-induced DNA

damage, cellular senescence, apoptosis, and emphysema [35, 36, 39]. The role for diminished MIF in the pathogenesis of emphysema is unclear, but several factors have been shown to contribute to the severe disease phenotype. First, MIF may promote the expression of a critical lung antioxidant, NRF-2, such that, low MIF levels could increase susceptibility to cellular oxidative damage [40]. Additionally, MIF is a repressor of the p16-RB and p53–21 cellular senescence pathways [36]. Increased cellular senescence is implicated in the secretion of pro-inflammatory cytokines and proteases involved in the pathogenesis severe COPD. Finally, *Mif*-knockout mice show reduced vascular endothelial growth factor (VEGF) VEGF signaling in response to oxidative stress, which results in reduced vasculogenesis, a finding implicated in the pathogenesis of COPD [41–43]. Ultimately, these findings suggest a central role for MIF in mitigating the consequences of oxidative damage in the injured lung and suggest a possible avenue for therapeutic intervention with MIF in patients with severe COPD.

3.2 Asthma

Asthma is a common type of chronic airway inflammation characterized by variable, reversible airway obstruction and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and dyspnea resulting from the contraction of tracheobronchial smooth muscle, hypersecretion of mucus, and mucosal edema [43].

Unlike COPD, expression of MIF is inversely correlated to clinical outcomes in asthma, as illustrated by a study in which MIF concentration was increased in the BAL of asthma patients relative to controls [44, 45]. MIF is stored in circulating eosinophils and contributes to the release of cytokines in response to physiologic asthma stimuli, such as interleukin-5 [46]. Additionally, staining of sputum cells revealed that MIF was co-localized with eosinophil peroxidase in the cytoplasm [47]. Functional MIF alleles that contribute to higher basal and stimulated MIF promoter activity are associated with more severe disease phenotypes [48, 49]. Notably, severe asthma is associated with corticosteroid resistance, and MIF has been shown to override the anti-inflammatory effects of corticosteroids, suggesting a potential therapeutic role for MIF antagonism in this disease [50]. Notably, there are both distinct and overlapping features of asthma and COPD, and the study of MIF in these disease reveals an interesting paradigm where increased MIF results in the deleterious inflammatory consequences seen in asthma and airway predominant COPD, whereas decreased MIF causes cellular senescence, apoptosis, and vascular attrition commonly observed in emphysema.

4 Cystic Fibrosis

Cystic fibrosis (CF) is a common and fatal genetic disorder caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. This disease is characterized by chronic buildup of thick mucus in the airways of the lung, followed by infections with *Pseudomonas* sp. and *Burkholderia* sp. gram-negative bacteria.

As discussed previously, *Mif*-knockout mice were able to clear, but not kill, gram-negative bacteria more effectively than in WT mice. Additionally, MIF activity results in the delayed apoptosis of neutrophils, thus promoting the survival of activated leukocytes that contribute to the inflammatory response [51]. Furthermore, there is a significant correlation between the *Mif* promoter polymorphism and clinical severity of cystic fibrosis. Those individuals with the low-expressing *MIF* allele showed decreased *Pseudomonas* sp. colonization, while those with the higher MIF producing alleles showed increased lung injury [52]. The tautomerase enzymatic activity of MIF is believed to be critical to the inflammatory response in the lung [53]. The pathologic finding of excessive inflammation and the positive clinical outcomes associated with reduced MIF expression suggest that targeting MIF may yield beneficial outcomes when treating the infectious consequences of CF.

4.1 Lung Fibrosis

Lung fibrosis is a respiratory disease characterized by lung tissue scarring. The causes of fibrotic lung disease are commonly genetic, idiopathic, secondary to autoimmune disease, or secondary to drug reactions. MIF is increased in the BAL of patients with idiopathic pulmonary fibrosis (IPF), and immunohistochemical analysis of lung tissue from patients with IPF demonstrated increased MIF in the epithelium and fibroblastic foci [54, 55].

In a mouse model of IPF, administration of the fibrogenic agent bleomycin results in increased *Mif* expression. Although an anti-MIF antibody was able to mitigate the acute effects of bleomycin-induced lung injury, there was no difference in hydroxyproline content or histopathological lung fibrosis scoring [56]. In a radiation-induced lung injury model, aged *Mif*-knockout mice are more susceptible than age-matched control mice. This finding was associated with decreased antioxidant production [57]. In murine models for hepatic fibrosis and chronic liver injury, the *Mif*-knockout mice showed decreased PDGF activation and increased protection from injury [58]. Currently, the role of MIF in lung fibrosis remains uncertain.

4.2 MIF and Lung Cancer

Lung cancer is the most common fatal malignancies in the developed world, accounting for over one million deaths annually. Chronic inflammatory diseases are associated with enhanced risk of cancer, and MIF may be a link between lung inflammation and cancer development.

Histologic studies of lung cancer have suggested a pathogenic role for MIF. In normal lung tissue, MIF mRNA and protein are observed in the bronchial and alveolar epithelium, endothelium, vascular smooth muscle, and alveolar macrophages. Conversely, in tissue derived from primary lung adenocarcinoma, MIF is more heavily concentrated in the alveolar epithelium relative to normal tissue concentrations [59]. Likewise, the presence of MIF in the nuclei of non-small cell lung

cancer (NSCLC) is correlated with a worse prognosis compared to malignancies without MIF. It was subsequently demonstrated that NSCLC that produce high levels of MIF mRNA were derived from patients who were heavy smokers [60]. Furthermore, MIF and CD74 are so prevalent in malignant pulmonary carcinoma that increased immunohistochemical staining of MIF and CD74 could potentially be a biomarker of the disease [61, 62].

There are multiple mechanisms by which MIF's biological function can lead to pulmonary malignancies. MIF expression induces AKT and ERK 1/2 activation, contributing to tumor growth, survival, and invasion. MIF also upregulates VEGF, resulting in increased angiogenesis. Implicated in this proangiogenic process is a CXC chemokine induced by peripheral blood monocytes [63]. MIF can act together with its homolog, D-dopachrome tautomerase, to promote CXC8 and VEGF activity in NSCLC [64]. Finally, MIF negatively regulates the cell senescence and tumor suppressor gene p53 and the Rb-E2F signaling pathway, resulting in increased cell proliferation and reduced growth limitation [36, 65–69]. MIF regulates cyclin-dependent kinases and E2F transcription during cell cycle and growth and may play a role in regulating the DNA damage response [70]. Interesting preliminary data shows that *Mif*-knockout mice exhibit increased levels of DNA damage relative to controls [35, 71].

5 Conclusion

There is a growing body of evidence that highlights the critical role of MIF in various respiratory disorders. MIF acts as a stress-mediated cytokine, activating cellular pathways to mitigate harm during certain infections or under conditions of oxidative stress. High levels of MIF may perpetuate pulmonary conditions in which chronic inflammation becomes detrimental. It may be that MIF is implicated in so many pulmonary diseases because it functions as a rheostat for critical biologic processes in the lung. Therefore, timing, context, and degree determine if MIF serves a beneficial or pathologic role. Therapeutic intervention upon the MIF signaling pathway will require a better understanding of the cell-specific consequences of MIF as well as the various downstream signaling pathways regulated by MIF. However, once elucidated MIF-based strategies offer immense diagnostic and therapeutic potential.

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