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Published in:
American Journal of Physiology - Lung Cellular and Molecular Physiology

DOI:
10.1152/ajplung.00521.2019

Publication date:
2020

The role of MIF in chronic lung diseases: looking beyond inflammation

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Running head: MIF in chronic lung diseases

Key words: MIF, COPD, asthma, pulmonary fibrosis, lung cancer.

Author contributions:

L.F.S. and A.S.G. performed literature research and drafted the manuscript. L.F.S. prepared figures. L.F.S., A.S.G., G.J.P. and B.N.M. edited, revised and approved final version of the manuscript.

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Abstract

Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that has been associated with many diseases. Most studies found in literature describe MIF as a proinflammatory cytokine involved in chronic inflammatory conditions, but evidence from last years suggests that many of its key effects are not directly related to inflammation. In fact, MIF is constitutively expressed in most human tissues and in some cases in high levels, which does not reflect the pattern of expression of a classic proinflammatory cytokine. Moreover, MIF is highly expressed during embryonic development and decreases during adulthood, which point towards a more likely role as growth factor. Accordingly, MIF knockout mice develop age-related spontaneous emphysema, suggesting that MIF presence (e.g. in younger individuals and wild-type animals) is part of a healthy lung. In view of this new line of evidence, we aimed to review data on the role of MIF in the pathogenesis of chronic lung diseases.

1. Introduction

Macrophage migration inhibitory factor (MIF) is a conserved protein found across eukaryotes, as illustrated by (84), which in mammals is known by its function as a pleiotropic cytokine. In humans, the MIF gene is located on chromosome 22 and contains around 840 bp, which leads to 115 amino acids and a 12.5 kDa protein (9). From its crystal structure it is known that the MIF protein assembles into a homotrimer with each monomer containing a $\beta-\alpha-\beta$ motif (Fig.1). Unlike most cytokines, MIF has enzymatic activity as a phenylpyruvate tautomerase and D-dopachrome tautomerase. Due to its sequence, structure and enzymatic activity, MIF was classified as a member of the tautomerase superfamily of proteins (20). To date it is still unknown whether the enzymatic activity of MIF plays a physiological role in mammals, and there are no known endogenous substrates for MIF enzymatic activity in mammals or other eukaryotes.

In contrast to the physiological role of MIF's enzymatic function *in vivo*, the role of its cytokine activity has been studied widely and it is known that MIF exerts many of its effects through binding to the surface receptors CD74, CXCR4, CXCR2 and CXCR7 (7, 54, 86). To date MIF has been investigated mainly in the context of inflammatory conditions. This particular focus is partly explained by how MIF was discovered. MIF was identified in the mid-1960s by Bloom and Bennett and was named after observing inhibition of macrophage migration due to a soluble substance produced by sensitized lymphocytes in the presence of an antigen (8). Despite its early discovery, most MIF studies started in the 1990s and most reports since then refer to MIF as a proinflammatory cytokine, although many other activities of MIF have been described since (35). Some authors have even questioned the key proinflammatory effect of MIF, i.e. MIF-induced TNF-α release (48). This effect is more likely to be caused by lipopolysaccharide contaminating the recombinant MIF used in studies showing proinflammatory effects of MIF. This suggestion supports the idea that MIF activity goes beyond inflammation and there is in fact evidence that MIF most frequently induces other effects such as induction of cell migration, induction of proliferation and inhibition of apoptosis. While these effects could indirectly promote inflammation when acting on proinflammatory cells, the effects *per se* are not proinflammatory. In addition to the evidence from research publications, the data available in protein databases (i.e. the Protein Atlas www.proteinatlas.org, the Proteomics Database www.proteomicsdb.org) suggest that MIF is primarily not a proinflammatory cytokine. When comparing MIF expression patterns to those of classic proinflammatory cytokines such as IL-6 it is clear that while IL-6 is expressed at intermediate levels and only in a few selected tissues, MIF is widely expressed across tissues and in some cases in high levels. While this evidence does not prove MIF's biological function, it suggests that it may not be proinflammatory because constitutive ubiquitous high expression of a proinflammatory cytokine would hamper homeostasis and would lead to tissue dysfunction and a higher incidence of chronic proinflammatory diseases. It is expected, however, that proteins involved in basic cellular functions (i.e. proliferation, migration) or in protecting tissue integrity are widely found across tissues. Moreover, MIF has been shown to be highly expressed during embryonic development (77, 78), suggesting that MIF is more likely to behave as a growth and/or protective factor than as a proinflammatory cytokine.

Surprisingly, despite being an ubiquitous and constitutively expressed protein, MIF-deficient mice have a normal development, a normal size and behavior, are fertile and do not appear to present tissue abnormalities in several organs (10). They do, however, develop spontaneous age-related emphysema and respond differently to the development of diseases such as asthma, COPD and lung cancer (61, 64, 81). Additional evidence also supports that MIF exerts special protective roles in the lung. For instance, in contrast to cardiac tissue, MIF protein levels appear to decrease in the lungs of aged mice (60, 77, 81). MIF knockout mice display higher levels of senescence markers in the lung (p16, p19, p53 and p21) compared to wild type mice, especially in old age (81). Furthermore, bronchoalveolar lavage from MIF-deficient mice display a decreased antioxidant activity compared to that of wild-type mice and the differences in antioxidant activity increase further as the mice aged (60). This suggests that in the lung MIF may actually play a beneficial role by protecting from tissue senescence and damage. With that in mind, it is clear why MIF dysregulation can be implicated in the development of chronic diseases in the lung.

Chronic lung diseases are conditions with persistent and long-lasting effects. They usually present with a complex pathogenesis, which complicates and delays their full understanding and the design of accurate therapies or cures. Chronic lung diseases affect millions of people worldwide and represent an economic burden for society by means of research, medical care, disabilities and deaths (1, 12, 36). Therefore, it is key to identify dysregulated pathways playing a role in chronic lung diseases that could be used in the future for the development of diagnostic tools or therapeutic strategies.

Here we review the available data on MIF levels in chronic lung diseases and on the biological activity described for MIF with the aim of understanding the versatile function of MIF in chronic lung diseases. For the sake of clarity, we focused on the effect MIF has at a general cellular level and not as a modulator of responses of immune populations. Moreover, due to the presence of MIF homologues in microorganisms we have decided not to include any evidence from infectious diseases, for a clear identification of the effects of mammalian MIFs and not the ones from microbial MIF homologues.

2. Chronic lung diseases and MIF

The lung is the primary organ of the respiratory system, composed of specialized cell types that provide structure and perform the necessary tasks for the lung to function properly (reviewed in (65)). It is estimated that we breathe 10,000 liters of air every day and with it we also take in airborne particles that can injure the lung, which in many cases do not come out again during exhalation. In healthy conditions these threats do not necessarily cause a problem due to the fact that the lung has evolved to balance responses to maintain homeostasis, whereby it responds efficiently to threats without causing an exaggerated response that hampers the respiratory process. However, when the threat becomes repetitive and/or when the conditions alter basic cell functions (e.g. ageing, genetic predispositions, immune disorders) the response of the lung to tissue damage becomes distorted and may lead to lung diseases (Fig. 2).

MIF has been associated with several chronic lung diseases including chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, lung cancer, and pulmonary hypertension. MIF's association with pulmonary hypertension has been described in detail in an excellent recent review by Jalce and Guignabert, and is therefore not discussed in our review (40).

There is broad evidence on altered MIF expression in chronic lung diseases compared to healthy conditions. However, the role that MIF plays in most of these chronic diseases has not been fully elucidated. In many cases MIF is thought to associate with the inflammatory processes that are part of these diseases, given that it is often described as a proinflammatory cytokine. However, the most frequently described activities for MIF *in vitro* or *in vivo* are induction of proliferation, promotion of cell survival by inhibition of apoptosis, and -unlike its name suggests- induction of cell migration. These effects have been described for lung cells but also for cells from other tissues (Table 1). The versatile effects of MIF can be caused by binding to surface receptors such as CD74 or by direct interaction with intracellular proteins such as p53, as shown in table 1 and discussed in a recent review by Jankauskas and colleagues (41). The overall contribution of MIF to the pathogenesis of these chronic diseases can therefore be due to one of these activities and will be defined by MIF's effects on cells promoting the disease state.

2.1 COPD

COPD is one of the most common chronic lung diseases, and according to the WHO is the fourth cause of death worldwide (95). The primary cause of COPD is exposure to cigarette smoke and/or air pollution.

The pathogenesis of COPD develops as an exaggerated inflammation in response to cell damage caused by the repetitive exposure to toxic components such as those found in cigarette smoke or air pollution (74). Exposure of lung epithelial cells to these toxic agents leads to epithelial cell injury. Due to the repetitive nature of the toxic exposure, persistent inflammatory and repair responses may occur, leading to the overall destruction of lung tissue, known as emphysema and to airway fibrosis associated with chronic bronchitis (89). The airflow limitation characteristic of COPD is therefore caused by a combination of bronchitis and emphysema, the presence of which varies between patients. COPD patients present with dyspnea, chronic cough, sputum production and a progressive decline of lung function determined by FEV_1 (Forced expiratory volume in 1 second) and FVC (Forced vital capacity), measured by spirometry. COPD is diagnosed as a lung function impairment when the FEV_1/FVC ratio is lower than 0.7 (32). The severity of COPD is then classified according to the loss of FEV_1 and is divided into four GOLD stages: 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe). Additional to the progressive course of the disease, COPD patients can develop exacerbations, which are defined as acute worsening of respiratory symptoms, usually associated with respiratory viral infections, and often leading to hospitalization and death (92).

Many mediators are involved in the complex pathogenesis of COPD. Regarding the role of MIF in COPD, there are four studies in patients and four in mouse models, directly assessing this association. In humans, two studies found higher levels of MIF in COPD patients, in serum, sputum and bronchoalveolar lavage macrophages (39, 80), while the other two studies found lower levels of MIF in COPD patients in plasma and in serum (24, 81). These studies appear to show a trend towards higher MIF expression in lung-derived samples but lower levels of MIF in circulation in COPD patients. This could suggest a role for MIF directly in the area affected by the disease, i.e. the lung. Accordingly, one study evaluating gene expression signatures in peripheral blood mononuclear cells in COPD patients found that MIF gene expression in these cells (i.e. circulating cells) positively correlated with FEV_1 and FEV_1/FVC values, meaning MIF expression in these cells was the lowest in patients with COPD with the lowest FEV_1 (4). Additionally, Russell and colleagues found that MIF levels in bronchoalveolar lavage macrophages and sputum (i.e. lung-derived samples) are the highest in COPD, intermediate in healthy smokers, and the lowest in non-smoking controls, suggesting that cigarette smoke is the cause of higher MIF levels (80). Results from *in vitro* studies are in line with this suggestion, as it has been shown that pulmonary endothelial cells exposed to cigarette smoke extract produced higher levels of MIF than untreated cells and that inhibition of MIF expression enhanced the sensitivity of these cells to cigarette smoke extract (19). This also suggests that the increase in MIF levels in the COPD lung may be a response to the cigarette smoke-related injury and that MIF release into the bronchoalveolar space is in fact aiming to protect cells from further damage.

The studies with COPD patients also show that MIF levels are affected by disease severity. One of the studies showing lower MIF levels in COPD serum also showed even lower MIF levels in patients with more severe COPD (24). Another study found that the 5 repeats of the MIF -794 CATT microsatellite, which leads to lower MIF gene expression, was associated with a decrease in diffusion capacity for carbon monoxide (DLCO), a measure of the gas exchange capacity of the alveoli (105). This is interesting because it has been shown that a lower DLCO is associated with more COPD symptoms (5). Additionally, MIF levels are also affected by exacerbations. Husebø and colleagues, who found higher MIF levels in COPD serum, showed that MIF levels were even higher during acute exacerbations (39). This suggests that an increase in levels of circulating MIF can be caused by an underlying exacerbation. Together, the observations in patients suggest that variations in MIF levels in COPD depend on the nature of the sample, GOLD stage, the types of components to which the patients were exposed (e.g. cigarette smoke), and whether patients presented exacerbations. Moreover, sample preparation has been shown to have an additional effect on the accurate and reproducible detection of MIF levels in human samples (83).

In mice, two studies using a mouse model of ozone-induced COPD found higher MIF mRNA and protein levels in lungs and bronchoalveolar lavage from ozone-exposed mice compared to the air-exposed mice (80, 96). A third study using a mouse model of cigarette smoke-induced COPD found lower MIF mRNA and protein levels in lung samples from cigarette smoke-exposed mice compared to air-exposed mice (24). The authors also found that MIF can protect endothelial cells from cigarette smoke-induced apoptosis. The fourth study found that the

response to cigarette smoke exposure was age-dependent and that while 3 month-old mice had higher MIF protein levels, 6 month-old mice had lower MIF protein expression in bronchoalveolar lavage (81). This study also found that MIF-KO mice develop age-related spontaneous emphysema and are also more susceptible to cigarette smoke-induced emphysema. This is supported by a study by Marsh and colleagues, in which they found that MIF induces type 2 alveolar epithelial cell proliferation via CD74, suggesting that in the absence of MIF the alveolar epithelium may not be efficiently replenished after damage (59). The data from these COPD mouse models suggest that MIF levels change depending on the model used and the age at the time of exposure. This is in agreement with what was observed in the COPD human studies, suggesting that MIF levels in COPD are affected by diverse variables.

Altogether, the studies on MIF in COPD suggest that MIF levels vary according to age, disease severity, exacerbations and origin of the sample (local vs. circulatory) (Fig. 3). However, throughout the data there is a pattern indicating that MIF levels increase locally in lung tissue upon exposure to cigarette smoke, especially at a younger age. Moreover, the inhibition, decrease or absence of MIF leads to an increased sensitivity to apoptosis and to lung tissue destruction, highlighting the protective and non-inflammatory role of MIF in COPD. This could explain why COPD severity associates with lower MIF levels, suggesting that in more advance stages of the disease, or perhaps older age, the protective mechanisms of the lung are less active. Of note, *in vitro* studies have shown that MIF promotes proliferation of fibroblasts and smooth muscle cells (51, 101, 104). This suggests that while MIF release may promote alveolar epithelium proliferation, preventing emphysema, it may also induce proliferation of fibroblasts and smooth muscle cells, possibly promoting the development of bronchitis. Therefore, MIF appears to support a pro-repair response in COPD, although more studies are needed to fully elucidate MIF's function and variable expression in the context of COPD.

2.2 Asthma

Asthma is a chronic inflammatory disease, affecting children and adults, characterized by airway obstruction and bronchial hyperresponsiveness (reviewed in (71)). Asthma is thought to develop as a complex gene-environment interaction in response to allergens, pollutants, microbes and/or oxidative stress. It is therefore a heterogeneous condition with diverse pathological features that lead to different endotypes of asthma. Overall, the different endotypes of asthma are all characterized by airway hyperresponsiveness, a consequence of immune and physiological responses to allergens or pollutants. The immune response in asthma patients may include activation of eosinophils, neutrophils, dendritic cells, macrophages, mast cells and CD4+ T cells of the T helper 2 type. Another distinctive pathophysiological feature of asthma is airway remodeling, characterized by thickening of the basement membrane, an increase in airway smooth muscle mass, bronchial epithelium damage and cilial dysfunction, goblet cell hyperplasia and increased mucus production. Together, in terms of airway function, these features translate to a hypercontractile airway with a poor barrier function and an immune system ready to respond. Consequently, asthma patients present with episodes of cough, wheeze, shortness of breath, and chest tightness (71). Although asthma has a lower fatality rate compared to other chronic lung diseases, it affects 300 million people world-wide and therefore is a major chronic disease (97).

Overall, the studies on MIF in asthma have found higher levels of MIF in asthmatic compared to control conditions. One study found higher MIF levels in bronchoalveolar lavage of asthma patients and found that activated eosinophils are an important source of MIF, as eosinophils stimulated with phorbol myristate acetate (PMA) produced high levels of MIF (79). Another study also found higher levels of MIF in serum and induced sputum of asthma patients, with the highest levels in symptomatic patients, intermediate in asymptomatic patients and the lowest in controls, suggesting that MIF levels are positively associated with disease severity (102).

Genetic studies have shown that the -173 G/C single nucleotide polymorphism in the MIF promoter influences MIF gene expression, with the C nucleotide leading to higher MIF gene expression than the G nucleotide. Two studies in Egyptian and in Northeastern Chinese population found significantly higher frequency of the MIF -173CC genotype in children with asthma, compared to healthy children (23, 98). This supports what was observed in the aforementioned studies with asthma patients, in which they found higher levels of MIF in patients compared to controls.

The studies in patients suggest that MIF levels are higher in asthma, and results from animal models for asthma not only agree with this finding but suggest that elevated MIF levels promote the pathogenic process. There are six studies using a mouse/rat model of ovalbumin-induced allergic lung inflammation. The majority of those studies found that ovalbumin-treated animals had higher levels of MIF than untreated animals and that upon MIF deficiency or inhibition, asthma features were significantly lower (i.e. eosinophil counts, neutrophil counts, airway hyperresponsiveness, airway smooth muscle thickness) (2, 13, 45, 58, 64). One of these studies also found that MIF-deficiency led to lower levels of Th2 cytokines (i.e. IL-5 and eotaxin) (64), but two other studies using anti-MIF antibodies did not observe an effect on the levels of these cytokines or IgE titers (45, 58). Additionally, one study using a model of house dust mite-induced allergic lung inflammation found that the use of MIF inhibitor ISO-1 ameliorated airway hyperreactivity, neutrophil and eosinophil counts, but also decreased the levels of Th2 cytokines and IgE titers (50). Given the fact that this reduction in IgE levels was observed in a different model than the one from other animal studies described above, it is difficult to discern whether this effect is model-dependent. Furthermore, the contrasting results on Th2 cytokines could be due to differential effects of MIF inhibitors versus anti-MIF antibodies on intracellular MIF levels, as anti-MIF antibodies would only influence extracellular MIF levels, while MIF inhibitors could potentially influence both. Future studies should confirm this hypothesis.

All together the studies of MIF in asthma, both in patients and in animal models, consistently show higher MIF expression in disease compared to control conditions (Fig. 4). Moreover, the data suggest that MIF expression positively correlates to disease severity and that MIF inhibition improves the pathological features. This is not surprising, as *in vitro* evidence suggests that MIF promotes the proliferation of airway smooth muscle and migration of eosinohils (22, 51), which can both contribute to asthma pathogenesis. However, it seems that MIF inhibition, unlike MIF-deficiency, has no effect on atopy-related features (i.e. IgE levels). Since many asthma patients have an atopic background, it is necessary to evaluate whether MIF inhibition can be beneficial

for those patients. Considering that the pathogenesis of asthma in a majority of patients and in most animal model is predominantly Th2-driven, the positive association of MIF with asthma suggests a role for MIF in Th2-related responses. Therefore, MIF in asthma positively associates with a lung allergic inflammation and not necessarily with classic Th1 inflammation.

2.3 Pulmonary fibrosis

Pulmonary fibrosis is a type of interstitial lung disease characterized by the accumulation of extracellular matrix in the alveolar interstitium. It can develop as the end-stage of other diseases such as scleroderma, due to the exposure of toxic components such as silica, or as a side effect of chemotherapeutic drugs such as bleomycin, but often its cause is unknown and is called idiopathic pulmonary fibrosis (IPF) (99). Here we focus mostly on IPF because it is the best characterized interstitial lung disease, the most common of the idiopathic interstitial pneumonias, and the one with most research studies.

Many types of pulmonary fibrosis, and especially IPF, do not present with an inflammatory component at the moment of diagnosis, but it is believed that fibrosis begins with lung injury (99). It is widely hypothesized that the pathogenesis of pulmonary fibrosis involves damage of alveolar epithelial cells and a subsequent exaggerated repair response (reviewed in (26)). The fibrotic lung is characterized by fibrotic foci formed by active and hyperproliferating fibroblasts that produce high amounts of extracellular matrix. Additionally, there is a predominant Th2 cytokine profile (e.g., IL-4, IL-13), produced by mast cells and other cells, that promotes the polarization of macrophages towards a pro-repair phenotype. The accumulation of extracellular matrix in the interstitium thickens the alveolar wall, and decreases the oxygen uptake contributing to organ dysfunction and ultimately to a lethal respiratory failure.

Pulmonary fibrosis is more likely to affect men than women and is more likely to occur in smokers. This disease has a prognosis of 3 to 5 years after diagnosis and to date there is no cure for this disease (76). Although in some cases lung transplantation is an option, this is not always possible or available for all patients. Additionally, there are two FDA-approved drugs for the treatment of IPF, i.e. nintedanib and pirfenidone, that slow down lung function decline although they do not fully halt the progression of fibrosis (72). There is thus an urgent need to identify therapeutic targets for this disease.

Among the different chronic lung diseases associated with MIF, pulmonary fibrosis was the first one to be described. In 1976 Kravis and colleagues showed that in the presence of collagen, peripheral blood lymphocytes from IPF patients produced more MIF than lymphocytes from control individuals (47). Three decades later another study found higher levels of MIF in bronchoalveolar lavage of IPF patients compared to control individuals (6). They also found MIF staining in lung tissue to be stronger in bronchial epithelium, alveolar epithelium and in fibroblast foci in IPF patients. This pattern is confirmed by another study from the same group in which they showed MIF expression in IPF lung tissue to be high in alveolar epithelium, bronchial epithelium, in epithelial metaplastic areas and in areas of active fibrosis; there was higher MIF expression in the peripheral zones of the fibroblast foci rather than in the central areas (69). The high expression of MIF in fibrotic foci is also supported by *in vitro* studies showing that

bleomycin-treated fibroblasts have higher MIF mRNA levels and release more MIF protein (16). This suggests that MIF expression increases in areas directly affected by fibrosis.

Two studies in a mouse model of bleomycin-induced pulmonary fibrosis have found higher MIF levels in lung tissue, serum, and bronchoalveolar lavage compared to controls (33, 85). Both studies assessed the impact of inhibiting MIF on the development of lung fibrosis. Tanino and colleagues used a neutralizing anti-MIF antibody and found less infiltration of inflammatory cells, lower levels of TNF-α, less lung injury, and less mortality, but not less collagen deposition. Günther and colleagues used MIF inhibitors in the bleomycin model and found that MIF inhibition led to less fibrosis (assessed by collagen deposition), lower pulmonary hypertension (assessed by percentage of muscularized pulmonary arteries) and fewer perivascular macrophages. These results suggest that MIF expression in fibrotic conditions is positively associated with features of a repair process (i.e. cell infiltration, cytokine levels and injury score) and may also be directly associated with fibrosis development, but that requires further testing.

While both human and mouse studies found higher levels of MIF in fibrotic conditions, it is not completely clear what role MIF is playing in the development of fibrosis. The mouse studies suggest that MIF inhibition may be beneficial by hampering features of fibrosis development. Nonetheless, the bleomycin model used in these studies develops with an initial inflammatory phase that later transforms into fibrosis, which may resolve later (87). Since inflammation is not a contributing factor to IPF, at least at the diagnosis stage, the high MIF levels in these patients may have a different source than inflammatory processes seen in the bleomycin model. One hypothetical option is that the high levels of MIF originate from senescent cells, as MIF production is higher in these cells(25), and higher expression of senescence markers has been found in lung tissue of pulmonary fibrosis patients (49, 82). In addition, a mouse study from Schafer and colleagues showed that bleomycin induces senescence in lung epithelial cells and lung fibroblasts and that the elimination of senescent cells improves pulmonary function and physical health (82). Their results also show that senescent fibroblasts have a profibrotic secretome. Considering that MIF has been described as a protein secreted by senescent cells, it is possible that MIF also contributes to the profibrotic effect of the senescent cell secretome (15). This, however, is a hypothetical scenario and requires further experimentation.

The evidence thus far points towards MIF playing a profibrotic and pathogenic role in pulmonary fibrosis (Fig. 5). Although based on a different pathogenesis, the evidence from asthma shows that MIF is associated with a Th2 (pro-repair) profile, which supports the association of MIF with fibrotic processes. This association could be pointing at a direct effect of MIF on fibrotic responses or at the fact that MIF influences other cells that contribute in some way to the fibrotic process. Such indirect effects could include MIF-induced migration and proliferation of immune cells that respond to lung injury, caused by bleomycin or otherwise. It is likely that MIF release influences different lung cells in various ways, as *in vitro* studies have shown that MIF can protect cells from cellular senescence and apoptosis (38, 70, 93, 100). While the high levels of MIF in pulmonary fibrosis could protect epithelial cells from senescence or cell death, the effect of MIF on immune cells and fibroblasts may be promoting a repair response that contributes to the development of fibrosis. However, we cannot conclude this with certainty yet and more

research is necessary to clarify the actual role of MIF in pulmonary fibrosis and the cell type-dependent effects that MIF can have in the context of fibrosis and fibrosis-associated senescence.

2.4 Lung Cancer

Lung cancer is the excessive and uncontrolled cell proliferation of lung epithelial cells (in most cases), eventually leading to impairment of tissue function, tissue failure, and death. A healthy cell can become cancerous after DNA damage leads to alterations in genes associated with DNA repair and regulation of cell growth (63). Such mutations can be caused by extrinsic factors (e.g. cigarette smoke) and intrinsic factors (e.g. radical oxygen species). Cancer cells will then have a characteristic uncontrolled growth, a higher invasive capacity, and an inability to respond to apoptotic stimuli. This will be accompanied by an increased ability to induce vascularization (angiogenesis) for the direct supply of nutrients to the tumor area (53).

Lung cancer is highly heterogeneous arising in many different sites in the lung, and can be classified as small cell lung carcinoma (10%-15% of lung cancer cases) or non-small cell lung carcinoma (85%-90% of lung cancer cases). Non-small cell carcinomas can be further classified as squamous cell carcinoma, usually originating in the main bronchi, adenocarcinomas, arising in peripheral bronchi, or large cell carcinomas, more proximal in location and with a rapid spread. Small cell lung cancers, on the other hand, derive from hormonal cells in the lung, are the most dedifferentiated cancers and are extremely aggressive (53).

According to the WHO, cancer is the second leading cause of death worldwide, and lung cancer is the most common type of cancer with an estimated 2,09 million cases in 2018. The survival rate for lung cancer is lower than for many other cancers and according to the U.S. National Institute of Health, more than half of the people with lung cancer die within one year of diagnosis (37). These statistics reflect the persistent need to develop appropriate tools for early diagnosis and therapeutic strategies for this disease.

Regarding MIF expression levels in lung cancer, there is a clear pattern of higher expression in cancer compared to healthy conditions. Studies on non-small cell lung cancer patients consistently show higher levels of MIF mRNA and protein in tumorous lung tissue, compared to regions of healthy tissue or to lung tissue from control individuals (30, 43, 88). Additionally, one of these studies found that higher MIF mRNA expression in patients with non-small cell lung cancer was associated with unfavorable prognosis (88). High MIF levels have also been shown to correlate with higher levels of angiogenic chemokines and higher vascularity and a subsequent increase in the risk of lung cancer recurrence (94). Interestingly, a study by Nolen and colleagues found that serum MIF levels in patients with non-small cell lung cancer can be used within a biomarker panel, including prolactin and thrombospondin, to effectively identify control individuals and lung cancer patients (67). This three-biomarker diagnosis model was shown to identify even control individuals according to the presence of pulmonary nodules with low and high levels of suspicion with around 90% specificity, showing its potential for the early diagnosis of lung cancer.

The evidence of higher MIF levels and correlation with poor prognosis in lung cancer patients demonstrates the importance of MIF in a clinical context but does not definitely prove that MIF is promoting cancer. Nonetheless, mouse studies on lung cancer show that if MIF levels are low, fewer or smaller tumors develop and that the presence of MIF during lung injury creates a suitable environment to potentiate the carcinogenic potential of mutated cells. One of such studies, by Arenberg and colleagues, was performed using mouse models of bleomycin- or naphthalene-induced lung injury. They found that injured lungs had high MIF levels and bigger orthotopic tumors (Lewis lung carcinoma, injected after lung injury) due to higher levels of proliferation and reduced apoptosis (3). This effect of increased tumor growth was not observed after lung injury in MIF-deficient mice, and MIF overexpression was sufficient to accelerate the growth of orthotopic tumors. Mawhinney and colleagues also confirmed the boosting effect that MIF has on cancer development with another mouse study of Lewis lung carcinoma. Their results show that primary tumor growth was significantly attenuated in MIF-deficient mice or mice containing a MIF variant with a mutation that blocks its enzymatic activity (61). While the relevance of MIF's enzymatic activity has yet to be elucidated, it is possible that a mutation that lowers this activity also affects MIF's conformation and/or its interactions with its receptors and other proteins. Moreover, *in vitro* studies with various lung cancer cell lines have shown that MIF overexpression promotes cell proliferation and that MIF inhibition or downregulation leads to a decrease in cell proliferation, cell migration and adhesion and to a higher apoptosis rate (18, 34, 56, 75, 107). Interestingly, MIF can be a target of miRNAs, some of which are expressed at lower levels in lung cancer tissue (and in lung cancer cell lines) compared to healthy tissue (e.g. miR-608 and miR-146a) (91, 103). Furthermore, a study by Yu and colleagues showed that the use of an inhibitor for miR-608 led to higher invasion and migration of cancer cells, which decreased significantly when MIF was downregulated (103). This evidence supports the observation that MIF promotes the invasion and migration of cancer cells and shows the potential of miRNAs as tools to decrease MIF levels and the pathogenicity of lung cancer cells. The positive effects of MIF on cell proliferation, apoptosis inhibition and cell migration have been shown in other cancer cell lines and in healthy conditions as well (Table 1). Combined these studies provide evidence that in the context of lung cancer, MIF can lead to promote the pathogenic features of lung cancer cells (i.e. proliferation, migration and adhesion), explaining the higher levels of MIF in cancer patients with a corresponding poor prognosis.

All human, mouse and *in vitro* studies on MIF in cancer consistently show that MIF levels are higher in lung cancer, that MIF presence is potentiating the proliferation and migration of lung cancer cells, and that MIF levels can be used as part of a biomarker panel for the diagnosis of lung cancer (Fig. 6). Therefore, it is wise that future studies test the use of MIF inhibition as a therapy to directly target cancer cells in the lung. Considering the roles MIF can play in healthy conditions, future tests of MIF inhibitory therapies for cancer treatment should also study the possible effects occurring from off-target MIF inhibition in healthy cells/tissues of cancer patients. Of note, MIF levels and its effects in cancer appear to be consistent across tissues (reviewed in (66)), suggesting that MIF inhibition is likely a therapeutic alternative for cancer in other tissues too.

3. Concluding remarks

The evidence presented here shows that MIF plays an important role in the pathogenesis of chronic lung diseases and that its role is not always proinflammatory as suggested before. MIF appears to be produced/released during tissue damage and can protect cells from toxicity of certain agents. In fact, there seems to be a stronger association of MIF with a pro-repair response (Th2) than with a proinflammatory response (Th1). This is observed in the pathogenesis of asthma and pulmonary fibrosis and confirmed by the fact that in the absence of MIF emphysema develops in mice. MIF release can also stimulate the migration and proliferation of immune cells, but does not necessarily lead to the production of proinflammatory cytokines.

While in some diseases like lung cancer the role of MIF is clearly pathogenic and there is potential for the development of a diagnostic or therapeutic tool, there is also a need for more research to fully elucidate the role of MIF in COPD, pulmonary fibrosis and asthma. A summary of the general conclusions regarding MIF and each of these diseases is shown in Figure 7. Due to the focus of this review we did not discuss the different effects MIF may have directly on immune cells. It is therefore important to elucidate whether manipulation of MIF levels may affect immune responses before moving forward with any MIF-related therapeutic strategy.

Moreover, MIF is not the only member of this protein family that appears to be involved in human diseases. The MIF homologue D-dopachrome tautomerase (DDT, also known as MIF-2) has been shown to share some activities with MIF, probably due to its ability to bind to MIF receptor CD74. In fact, there is evidence that MIF and DDT can work in a synergistic manner and there are a few studies showing a positive association of DDT with lung cancer (11, 14). However, DDT and MIF only share 34% sequence identity despite the fact that they have similar overall structures. It is therefore likely that MIF and DTT participate in different molecular interactions and signaling cascades. This highlights the importance of future studies elucidating the role of DDT in other chronic lung diseases as well and discovering how it functions together with or in comparison to MIF.

Future studies on MIF in lung diseases should also consider studying the cell-specific effect of MIF and whether the role of MIF differs in disease endotypes. Moreover, it is important to evaluate whether MIF can be used as a therapeutic strategy for chronic lung diseases. There is currently an ongoing clinical trial of an anti-MIF antibody for the treatment of solid intestinal tumors (ClinicalTrials.gov Identifier: NCT01765790); it is thus likely that there are more MIF-related trials on the horizon. Given the evidence shown here, future research in these areas should consider and test the possibility that MIF inhibition in the lung may promote the development of emphysema or other lung alterations. Further investigation in this area should elucidate in what way MIF manipulation can work as a therapeutic strategy for chronic lung diseases.

Disclosures

The authors have no conflicts of interest to disclose

FIGURE LEGENDS

Figure 1. MIF structure and β–α–β motif. A) *MIF tertiary structure viewed from the top. Each color represents one monomer.* ***B)*** *MIF tertiary structure viewed from the side.* ***C)*** *Representation of a beta strand-alpha helix-beta strand motif (β–α–β) present in proteins from the tautomerase superfamily. The structure of MIF (PDB ID 1MIF)[3] was obtained from the RCSB protein database (www.rcsb.org).*

Figure 2. Structure and composition of a healthy lung and alterations leading to chronic lung diseases. *The lung is composed of alveoli and airways. The airway epithelium is composed of specialized cells such as ciliated cells, goblet cells and basal cells. The alveoli are formed by type I and type II alveolar epithelial cells. The lung also contains macrophages that patrol the tissue and air spaces to protect from infections and harmful particles. They are found in the alveolar space -alveolar macrophages- or in the interstitial space -interstitial macrophages-. Exposure to cigarette smoke, air pollution, carcinogenic components and allergens can lead to alterations in lung structure and function and to the development of pathogenic conditions. Alterations in the alveolar structure are associated with pulmonary fibrosis and COPD. Airway alterations are associated with COPD and asthma. An uncontrolled proliferation of lung epithelial cells, caused by mutagens, is associated with lung cancer.*

Figure 3. Pathological features of COPD and evidence of MIF expression in COPD from human, mouse and in vitro studies. *BAL: Bronchoalveolar lavage. MIF-KO: MIF knockout (mouse). CS: Cigarette smoke.*

Figure 4. Pathological features of asthma and evidence of MIF expression in asthma from human, mouse and in vitro studies. *BAL(F): Bronchoalveolar lavage (fluid). PMA: Phorbol myristate acetate. OVA: Ovalbumin. HDM: House dust mite. MIF-KO: MIF knockout (mouse).*

Figure 5. Pathological features of pulmonary fibrosis and evidence of MIF expression in pulmonary fibrosis from human, mouse and in vitro studies. *BAL: Bronchoalveolar lavage*

Figure 6. Pathological features of lung cancer and evidence of MIF expression in lung cancer from human, mouse and in vitro studies.

Figure 7. Overall (non-inflammatory) contribution of MIF to the pathogenesis of COPD, asthma, pulmonary fibrosis and lung cancer

572 ***Table 1. Most frequently described functions of MIF and cell types it affects in the lung and in***
573 ***other organs.***

	Lung				Other organs			
	Cell type	**Mechanism / pathway reported ***	**Species**	**Reference**	**Cell type**	**Mechanism / pathway reported ***	**Species**	**Reference**
Proliferation	Lung cancer cell lines H524, H358, JL-1, DM-3, H28, H2052, H2452, MSTO, A549 and H460	Via CD74	Human	(18, 34, 56, 75)	Cancer cell lines 293T, MCF7, HCT116, Capan 2 and Panc1, MGC-8226, Hela, SiHa, RPMI-8226, Glioblastoma cells.	Stabilizes the p53-Mdm2 binding, avoiding p53 phosphorylation; Induces the expression of cyclin D1; inhibition of p27(Kip1) expressionl via the PI3K/Akt pathway	Human	(28, 29, 42, 44, 55, 90)
					Primary human umbilical artery smooth muscle cells		Human	(27)
					Neural stem progenitor cells & Cardiac stem cells	By increasing nuclear β-catenin expression; By activation of the PI3K/Akt/mTOR and AMPK pathways	Mouse	(17, 68, 106)
	Smooth muscle cells	By p21 downregulation; cyclin D1, cyclin D3, and Cdk6 upregulation; MEK, ERK1/2 and JNK phosphorylation	Rat	(51, 104)	Retinal pigment epithelial cells; Keratinocytes	Via phosphorylation of p38 and ERK signaling pathways	Human	(31, 73)
	Type II alveolar epithelial cells	Via CD74	Mouse	(59)	Cardiac fibroblasts	Via Src kinase signaling pathway	Rat	(101)
Cell survival / protection / anti-apoptosis	Human pulmonary macrovascular endothelial cell	Via p53 inhibition	Human	(19)	Cancer cell lines MCF-12A, MCF7, ZR-75-1, MDA-MB-468, HepG2, HCT116, Hela, Capan2 and Panc1	Via MIF-CD74 interaction and subsequent activation of PI3K/Akt; Via regulation of Bax, Bcl-xL, Bcl-2, Bad, Bax, and p53	Mouse / Human	(21, 29, 57)
					Neural stem progenitor cells	Via Bcl-2 and Bcl-xl activation	Mouse	(68)
	Smooth muscle cells	By increasing Bcl-xl and decreasing Bax	Rat	(51)	Mesenchymal stem cell	By inhibiting oxidative stress and activating the PI3K-Akt signaling pathway	Rat	(100)
					Cardiomyocites / Cardiac fibroblasts		Mouse	(46, 62)
Migration	Smooth muscle cells	By upregulating the expression of MMP-2	Rat	(51)	Primary Human Umbilical Artery Smooth Muscle Cells		Human	(27)
					Cancer cell lines Capan 2, Panc1, Hela, SiHa, JJ012	By decreasing e-cadherin and increasing Vimentin; By increasing avb3 integrin through PI3K/Akt/NF-kB	Human	(29, 52, 90)

					Eosinophils		Human	(22)
					Neural stem progenitor cells	Via CD74	Mouse	(68)

574 ** Mechanism / pathway reported by at least one of the studies*
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Figure 1.

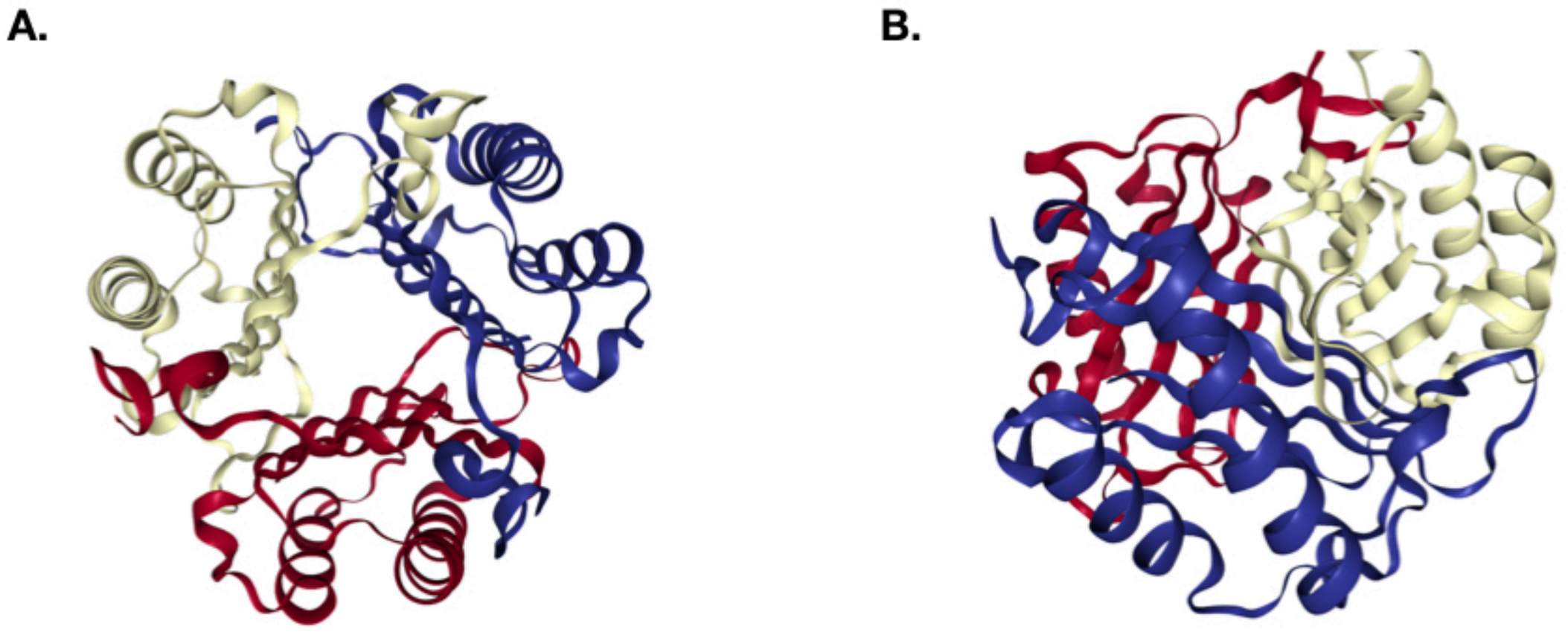


Figure 2.

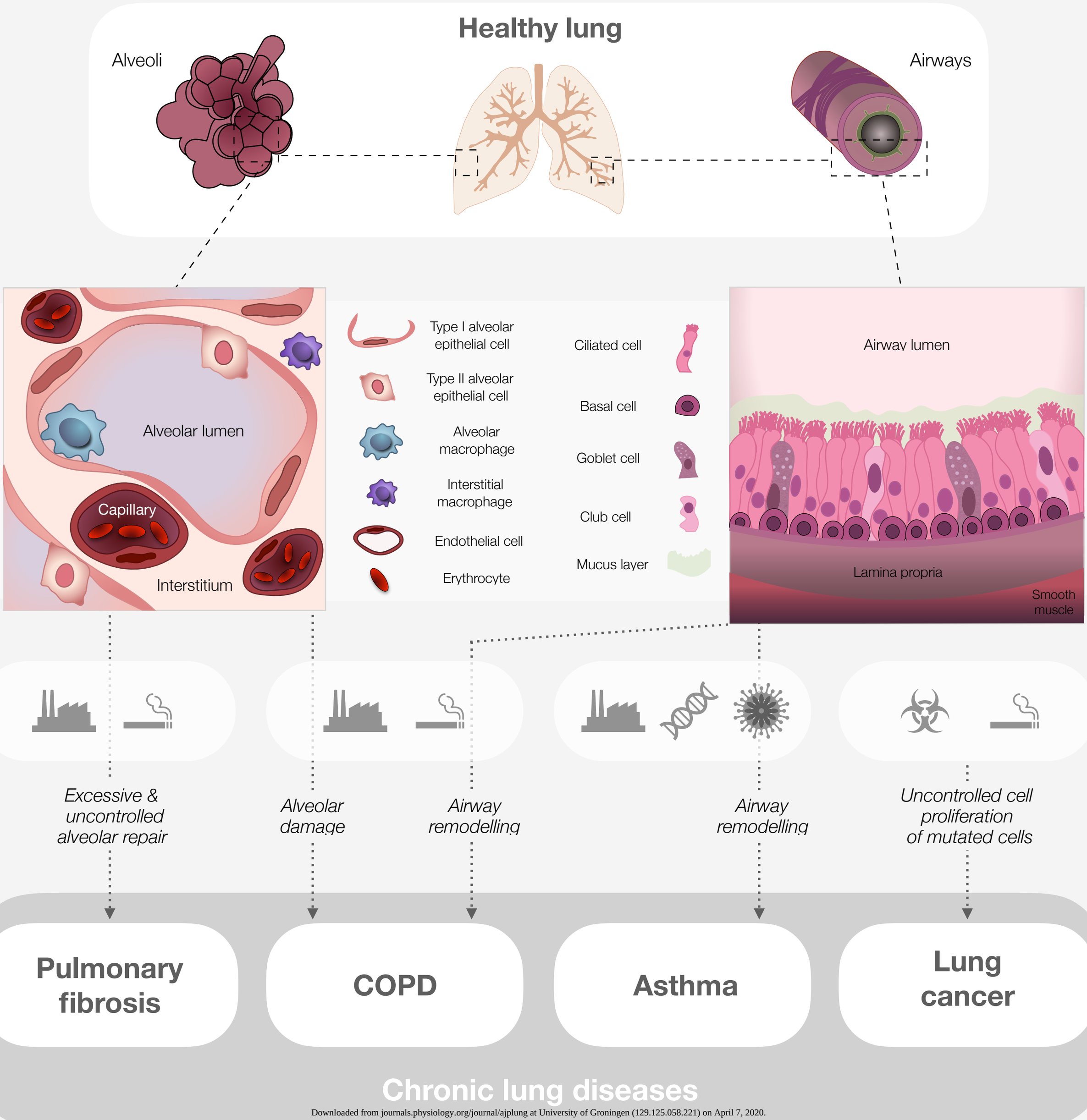
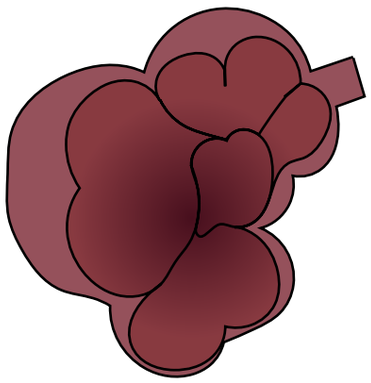


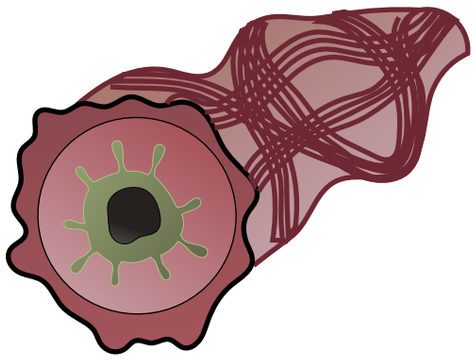
Figure 3.

COPD



Emphysema

- Alveolar destruction
- Loss of elastic recoil



Chronic bronchitis

- Airway inflammation
- Peribronchiar fibrosis
- Smooth muscle hyperplasia
- Mucus hypersecretion

MIF levels

- Sputum*
- BAL macrophages*
- Serum#

* COPD>smokers>controls
# even higher with exacerbations

- Plasma
- Serum*

* Even lower with high GOLD stages

- Ozone model (lung, BAL)
- CS model (young mice)

- CS model
- Old mice

Effects of MIF / MIF manipulation

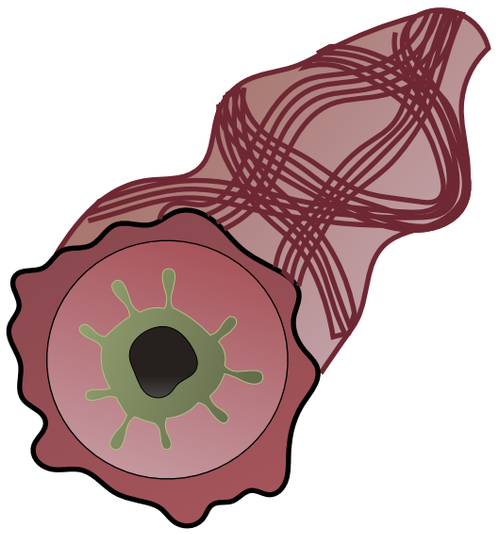
MIF-KO mice: susceptible to emphysema

- MIF induces proliferation of fibroblasts, smooth muscle cells, type II alveolar epithelial cells

- MIF protects from CS-induced cell death

Figure 4.

Asthma



- Smooth muscle hyperplasia
- Goblet cell hyperplasia
- Mucus hypersecretion
- Subepithelial fibrosis
- Bronchial hyperresponsiveness

MIF genetics

-173 CC genotype (high MIF expression):
More frequent in asthmatic children

MIF levels

- BAL (high in PMA-stimulated eosinophils)
- Serum*
- Induced sputum*

* symptomatic>asymptomatic>controls

- OVA model (Lung, BALF)
- HDM model (BALF)

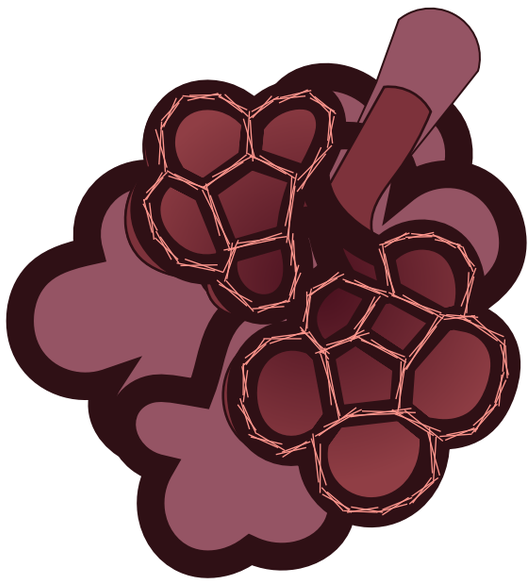
Effects of MIF / MIF manipulation

MIF-KO /MIF inhibition led to lower:
- Airway hyperresponsiveness
- Tissue eosinophilia
- Mucus metaplasia
- Levels of IL-13, eotaxin, cysteine leukotrienes and IL-5

- MIF induces proliferation of fibroblasts
- MIF induces proliferation of smooth muscle cells
- MIF induces migration of eosinophils & neutrophils

Figure 5.

Pulmonary fibrosis



- Interstitial fibrosis
- Fibroblast foci
- Increased tissue stiffness

MIF levels

- Peripheral blood lymphocytes
- BAL

- Bleomycin model
  - Lung
  - BAL
  - Serum

Effects of MIF / MIF manipulation

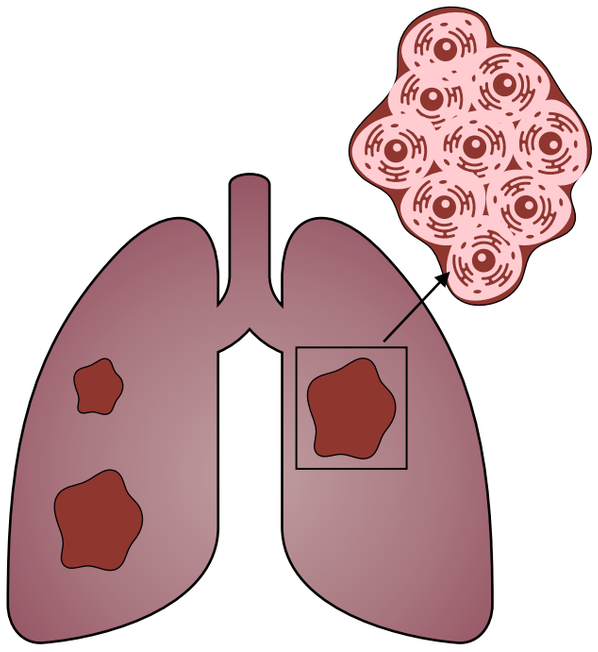
MIF inhibition led to lower:

- Cells infiltrating the alveoli
- Lung injury
- Mortality
- Perivascular macrophages
- Fibrosis (collagen deposition)

- MIF induces proliferation of fibroblasts

Figure 6.

Lung cancer



- Excessive and uncontrolled proliferation of lung cells

MIF levels

- Lung tissue
- Tumor area (vs. healthy region)
- Serum

- Bleomycin-induced lung injury
- Naphthalene-Induced lung injury

Effects of MIF / MIF manipulation

MIF inhibition: Attenuates tumor growth

MIF inhibition reduces cancer cell proliferation, migration, and adhesion

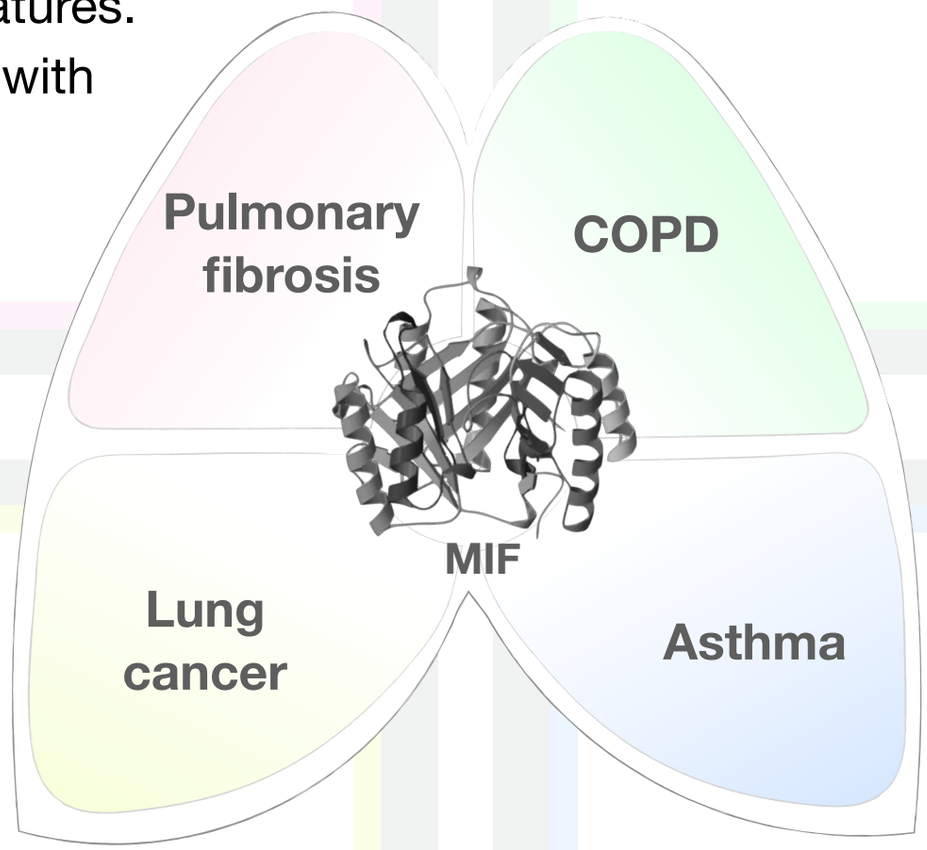
MIF in prognosis / diagnosis

- High MIF levels: worse prognosis
- MIF can be used as part of a panel to identify lung cancer patients

Figure 7.

MIF induces fibroblast proliferation and is associated with fibrotic features. MIF may also be associated with cell senescence related to pulmonary fibrosis

MIF induces cell proliferation and protects from cell death. It can protect from emphysema and promotes a pro-repair response, which may contribute to bronchitis and airway remodeling



MIF promotes the migration, proliferation and adhesion of lung cancer cells. MIF levels can be used as a diagnosis and prognosis tool in lung cancer

Polymorphisms leading to high MIF expression are frequent in asthmatics. MIF inhibition ameliorates features of allergic lung inflammation in mice