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MACROPHAGE MIGRATION INHIBITOR FACTOR AND IMMUNOCOMPETENT CELL OF LUNGS

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ABSTRACT

Migration inhibitory factor (MIF) is an emerging focus of immunoregulation cytokine in the crossroads of the nexus of infection, inflammation, fibrosis, and neoplasm in the lung, at the junction of the nexus of infection, inflammation, fibrosis, and lung cancer. The knowledge underlining the suggestion of MIF as a context-specific immunometabolic regulator in the airway milieu of the lung is summed up within this paper. We report on the structural biology, receptor binding, and signaling of the ERK, PI3K/AKT, NF-κB, STAT3, and HIF-1 signal transduction pathways. No less emphasis is laid on the process known as MIF-proton-mediated remodeling of immunocompatible lung immunocytes, i.e., neutrophils, dendritic cells, T lymphocytes, alveolar and interstitial macrophages, and innate lymphoid cells. MIF is associated with the presence of hypoxic stress, metabolic reorganization, and engagement of immunological checkpoint reorganization in acute infections, chronic inflammatory disease, fibrotic disease, and tumor expansion. Lastly, the implications on translation, such as translation of biomarkers, translation of mechanisms of therapeutic targeting, and advanced systems of modeling, are included. This review indicates by all analyses that MIF plays a significant role in the organization of lung immunological homeostasis as well as the development of the disease.

KEYWORDS: Macrophage Migration Inhibitory Factor, Lung Immunology, Cytokine Signaling, Hypoxia, Inflammation, Tumor Microenvironment

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1. INTRODUCTION

1.1 The Lung as a Specialized Immunological Organ

As one of the most immune-active organs of the human body, being in permanent contact with air infections, allergies, microbiological products, and particles of the surrounding environment, the lung is subject to numerous diseases. Rather than a passive barrier, epithelial cells of the airways act as an active secretion and release of cytokines, as they are the primary defense point [1]. DAMPs are also produced in infection and tissue injury and increase immunologic vigilance in the area [2]. It is also known that the networks of the innate immunity Inflammatory remodelling of airways is also altered by continuous antigenic stimulation, as has been recorded by the chronic inflammatory diseases like COPD [3]. More so, both the innate and adaptive cells work together in keeping the immune vigilance even against sustained exposure to lung infections such as non-tuberculosis mycobacterial disease [4]. The immune level of surveillance on the tissue level also highlights the fact that the lungs could be immunologically prepared and reach the latent stage of the virus management process [5]. In case this is coupled with constant exposure, the tight control of the pulmonary immunity is carried out to avoid the tissue damage that is excessive. Whereas the endothelial-immune cell communication is engaged in the control of leukocyte traffic and leukocyte demise [7], there are immunosurveillance and immunoediting processes that accommodate tolerance against the rapid effect of the immune cells [6]. Host immunological status plays a pivotal role in determining the amount of inflammation as it is expressed in opportunistic infections like Pneumocystis pneumonia [8]. The formation of a tissue-resident immune population with development can also be used to support long-term compartmentalization regulation [9]. It is structurally enhanced by compartmentalization of the lung into two compartments (alveolar and interstitial) as an immune organ, which exerts diversification between the alveolar and interstitial macrophage niches [10, 12].

1.2 Discovery and Evolution of MIF

Macrophage migration inhibitory factor (MIF), a direct T-cell product, has developed into a T-cell product comprising multiple functions as a pleiotropic immunomodulatory, inflammatory, and tumor biology performance factor. Recent research also reported that MIF and its analogue D-dopachrome tautomerase (D-DT, also known as MIF-2) experience functional diversification alongside the conventional inflammatory signaling and could be involved in carcinogenesis [13]. MIF is being shown to be a Janus-headed cytokine that is capable of simultaneously mediating pathological inflammation in viral infections and host defense [14]. The MIF family of cytokines affects most of the oncology hallmarks and includes angiogenesis, proliferation, immune evasion, and metabolic reprogramming [15]. Further proof that the MIF activities prove to be immensely context-dependent in space is that different patterns of heterogeneous expression are seen in tumors [16]. The discovery that MIF is by its nature an enzyme (tautomerase) that discriminates MIF over traditional cytokines was an important conceptual one. Stress-adaptive signaling pathways include MIF, as the association with the stress-adaptive elements in conditions of molecular chaperone stabilization like Hsp90 enables tumor growth and macrophage recruitment [17]. Its significance in the immunological microenvironment development is further indicated through its different subgroups that vary in the expression of receptors [18]. According to the pharmacologic inhibition, MIF might change the tumor progression and events of inflammatory changes, and it was known to be biologically relevant [19]. Besides cancer, MIF has been linked with the physiologic pathophysiology of lung adenocarcinoma [20] and COVID-19 dysregulation of immunology [21], and all these cultures highlight that it has wide application in both inflammatory and malignancy pulmonary disease models.

1.3 Rationale and Scope of This Review

The roles of MIF in the immune compartment of the lung need to be placed in a contextualized comprehension, notwithstanding that the mechanism has been thoroughly examined in systemic inflammatory disease and malignancy. The pulmonary milieu is comprised of circulating leukocytes, the resident segment of macrophages, vascular interfaces, and epithelial barriers in particular. The importance of such an immune control at the organ level is given the recent evidence that shows that the macrophage reprogramming leading to the development of the inflammatory responses by infection can have an effect on the lung tumors [23]. Further, the influence of the local microenvironmental factors on the polarization of the immune cells and response to treatment is shown with the help of the tumor immune heterogeneity in the non-small cell lung cancer [24]. Together with our results, the lung musculature architecture size and immunodynamics must be accounted for during extrapolation of the MIF signaling on systemic

paradigms usage. Theoretically, the recommendation of MIF as the context-dependent immunoregulator of the lung system is suggested in this review. MIF is not merely a pro-inflammatory mediator but the mediator of metabolic adaptation, hypoxia-induced metabolic signaling, immune cell recruitment, or tissue remodelling. It also has the ability to integrate the stress-induced signaling with the immunology effector programs that are based on its intracellular activities, its enzymatic activity, and its receptor functions (the CD74 and the chemokine receptors). This integrative power is of great significance, especially in the lung, where the hypoxia gradients, exposure to microbes, and tumor-associated variables co-exist. Therefore, in this narrative research, a mechanistic perspective has been followed contrary to a meta-analytical perspective. The current paper will summarize the current developments (2020–2025) to address the role of MIF in alveolar and interstitial macrophage, neutrophil, dendritic cell, lymphocyte, and innate lymphoid cell homeostasis and pulmonary disease control. We are supposed to unveil an idea model that later can be applied in the translational targeting of lung cancer, fibrosis, acute damage of lungs, and virus infection by focusing on molecular pathways and cell-specific effects.

2. MOLECULAR BIOLOGY OF MIF: STRUCTURE, RECEPTORS, AND SIGNALING

2.1 Structural and Biochemical Features

The presence of a great enzymatic tautomerase potential and extracellular and intracellular traits makes the structural aspect of macrophage migration inhibitory factor (MIF) not similar to that of the other cytokines. It is also increasingly emerging as this catalytic domain is structurally associated with receptor activation and downstream signaling even though the physiological target of its tautomerase activity remains disputed. Biological applications to the enzymatic arrangement of MIF-dependent inflammatory amplification have associated morphological modification in the macrophages in response to the infection with implications for the biological significance of MIF in the sustenance of immune responses [25]. Along with catalysis, MIF has redox reactivity that allows the responsive reaction of the oxidative stress to the inflammatory tissues and the influence of the condition of production of cytokines and the condition of the macrophage activation [25]. More to the point, MIF has external and internal operations. It controls the survival and stress metabolic responses of cells by communicating with signaling intermediates in the intracellular space. MIF that is released extracellularly rearranges the tumor microenvironment and immune evasion via autocrine and paracrine feedbacks. Indicatively, the release of MIF by the cancer stem cells to mediate the reprogramming of metabolism and suppression of anti-tumor immunity has been verified [26]. The MIF expression of lung adenocarcinoma has been found to be heterogeneous, accompanied by tumor multiplicity, meaning that there is the presence of extracellular signaling niches, geographically separate [27]. All these findings emphasize the fact that the structural peculiarities coupled with the functional plasticity of MIF are integrable, which allows it to incorporate compartment-specific signaling, redox-sensing, and enzymatic active domains.

2.2 MIF Receptors and Co-receptors

The MIF receptor exhibits a high-affinity receptor, CD74, which is the mediator of the biological activity of MIF. The augmented interaction of CD74 with the downstream signalling mechanisms of macrophages' recruitment, survival, and amplification. Even though not detected in the reduced tumor-macrophage interactions in lung adenocarcinoma, the CD74-related genetic variations have been found to signify the relevance of the receptor in the immune microbial surroundings of lungs [28]. However, co-receptor interaction is an essential part of full transmission of signals, and CD74 signaling is not a solitary interaction. Considering CD44 as a significant signaling partner, receptor clustering and cytoskeletal reorganization are regulated. The CD44 molecular bridge is an intermediary between extracellular matrix remodeling and immune activation that integrates the fibrotic and inflammatory signaling pathways along with it as a supporting mechanism [29]. The propagation of metastases of the lung cancer environments are reinforced by the interaction of the STAT3-centered immunologist circles with the receptor-mediated signaling circles [30]. The non-cognitogenic chemokine-like behavior of MIF uses CXCR2, CXCR4, and CXCR7 in addition to CD74/CD44 complexes. According to such interactions, MIF is also capable of functioning as a chemokine receptor and stimulating communication between tumor and stroma and cell migration [31, 32]. This type of receptor lethargy increases the spatial response of MIF signaling in hypoxic or inflammatory tissue. Also, there is signaling divergence in context exhibited by the homolog D-dopachrome tautomerase (MIF-2) under specific circumstances

only in viral and inflammatory deals, but with common receptor use [33]. The receptor is a flexible one, and that is why the immunomodulatory options of MIF in pulmonary disease have such a massive spectrum.

2.3 Downstream Signaling Cascades

Upon contact with its receptors, MIF triggers a series of intracellular signaling pathways that have overlapped with inflammation, survival, and metabolic adaptability. One of the initial responses involving ERK1/2 phosphorylation to incorporate does the integration of the activation of MIF with macrophage coordination and cytotoxic T cells in the tumor milieu [34]. NF-κB association: Macrophage immune suppression by tumor-associated macrophages is enhanced by NF-κB association, which is enhanced by crosstalk and enhances pro-inflammatory transcriptional programs [35]. Being a trendsetter, MIF causes a great deal of inflammatory loop activation as it involves ERK and NF-kB pathways. There are also MIF interactions with the PI3K/AKT pathway, which is a signaling axis that is strongly allied with myeloid cell recruitment and immunological resistance. Non-small cell lung cancer PI3K/AKT signaling is closely associated with PI3K/AKT-regulated immune escape that is dependent on the infiltration of myeloid-derived suppressor cells [36]. At the same time, the proinflammatory gene expression is maintained, and the macrophage polarization state is predetermined by the simultaneous activation of NF-κB [37]. MIF also interacts with the STAT3 signaling that is necessary in the M2-like macrophage polarization and resistance to treatment and not part of these classical cascades [38]. Hypoxia-responsive signaling also increases its effects. Manipulation of the polarization of macrophages during stress leads to pro-tumoral inflammation [40], although the HIF-1 alpha axis promotes tumor growth and plasticity of the macrophages under low oxygen conditions [39]. Lastly, and with effects on the glycolytic flux and transcriptional responses that govern the cellular energy homeostasis, MIF helps to rearrange the metabolism of the immune cells, aligning the metabolic demands of the inflammatory response [41]. The combination of these interconnected pathways makes MIF a central controller with the inclusion of hypoxia, inflammation, and metabolic remodelling of the lung microenvironment.

Table 1: MIF Receptors, Co-receptors, and Major Signaling Pathways in Lung Immunocompetent Cells

Category	Key Molecules	Representative Pathways	Functional Outcome	Ref. Sl. No.
Primary receptor	CD74	ERK1/2, PI3K/AKT	Effector T cell expansion, macrophage activation	[28]
Co-receptor	CD44	STAT3, NF-κB	Fibrosis modulation, inflammatory amplification	[29]
Chemokine receptors	CXCR2, CXCR4, CXCR7	MAPK, PI3K/AKT	Leukocyte trafficking, tumor cell migration	[32]
ERK1/2 axis	Downstream of CD74	ERK1/2 phosphorylation	TAM orchestration, T cell immunity	[34]
STAT3 axis	CD44 cooperation	STAT3 activation	Overcomes EGFR resistance, suppresses M2 macrophage polarization	[38]
HIF-1α axis	Hypoxia-linked signaling	HIF stabilization	Pro-tumor macrophage polarization, metabolic adaptation	[40]

3. MIF IN LUNG IMMUNOCOMPETENT CELL POPULATIONS

3.1 Alveolar Macrophages

The self-renewing sentinel is the long-lived alveolar macrophage (AM), which is sampling the inhaled pathogens and particles all the time and preserving the lung homeostasis. They occur in the lumen of the alveoli and control early antiviral and antibacterial reactions and overproduction of inflammatory reactions to ensure the continuity of gas exchange [42]. MIF will play an important role as an immunomodulator in such a strictly regulated environment. MIF can be used to boost host defense responses in case of an acute infection that involves improvements in the concentration of pathogen-surface markers of inflammatory cytokines (macrophages). Alternatively, constant or incessant stimulation may cause a transition from protective to tissue-damaging inflammation. The classic polarization of the M1/M2 paradigm is rather simplistic about AM functional diversity. Recent evidence sustains many different levels of activation, which are regulated by local cytokines, metabolic programming, and gradient of hypoxia. MIF allows this pliability to coordinate the inflammatory phenotypes, allowing the inflammatory phenotypes to be reprogrammed to become stable and regulating the metabolism of macrophages and the inflammatory effector functions. MIF is capable of cooperating with the hypoxia-reactive mechanisms and also plays a role in the maintenance of the macrophage activation and cytokine amplification of hypoxic niches of the alveoli, which are frequently seen in cases of infection, tumor growth, or acute

lung injury. Therefore, metabolic status, environmental stress, and immune response interact through MIF as a setting-dependent controller in the alveolar compartments in addition to it being a pro-inflammatory cytokine [42].

3.2 Interstitial Macrophages and Monocyte-Derived Macrophages

The interstitial macrophages (IMs) and the monocyte-derived macrophages (MDMs) possess varied niches of existence in comparison with the alveolar macrophages. The Ims, which exist in the pulmonary interstitium, control the vascular-immune interfaces and participate in the surveillance of antigens. Inflammatory or infectious states attract adhesive monocytes of chemokine gradients, specifically CCL2-CXCR. These monocytes then become macrophages, which alter the local immunity. One of them is the Trem2-high interstitial macrophage whose active development has been noted during the Pneumocystis infection, questioning the plasticity and inducibility of this compartment [43]. MIF has a chemokine-like behavior, and in addition to this, receptors make contact as well as have the capacity to regulate this cascade of recruitment that can lead to the aberrant infiltration of monocytes into the timing of inflammatory or pre-neoplastic pulmonary tissue. The recruited macrophages would transform themselves to be pro-angiogenic and immunosuppressive in tumor spaces, which promotes the colonization of metastases. MIF would also be effective in establishing a pre-metastatic niche enabling inflammatory signaling and a metabolic adjustment environment to allow tumor cell survival. The interstitial macrophages are essential in controlling the capacity of leukocytes to homeostatically regulate the extracellular matrix remodeling according to their positional location in the vicinity of the vasculature. In this connection, MIF-mediated signaling may trigger structural remodeling along with inflammatory amplification where there is a long-term tissue reorganization that is associated with the immune response as a reaction to infection. Therefore, there is a probability that MIF will affect the structural and immunological reorganization of the lung interstitium, along with the macrophage differentiation [43].

3.3 Neutrophils

The neutrophils are the quick recruiting effector cells, and they significantly contribute to the antimicrobial defense of the lung during the initial stages. They are all associated with the arsenal of antimicrobials, degranulation, production of reactive oxygen species, and building of neutrophil extracellular traps (NETs). Although NETosis is a defense of the person against pathogens, it is also a two-sided weapon; excess levels of NET have been observed to lead to thrombosis, epithelial damage, and eventually chronic inflammation [44]. In this aspect, MIF can result in neutrophil recruitment and activation upregulation. MIF is potentially involved in improving neutrophil chemotaxis and retention in vascular inflammatory lung tissue, which binds to chemokine receptors, including CXCR 2. Continuous neutrophil inflammation inflames the inflammatory lesions in the local area, as well as multiplies the likelihood of the formation of NETs. In addition, neutrophils and macrophages can also share the communication to form a feed-forward inflammatory loop. The neutrophile products can complement the action of the macrophage productions, and the neutrophil products can facilitate the stimulation and survival of the neutrophils. Both types of cells produce MIF and are capable of stimulating this mechanism of mutual stimulation and providing a tilt towards the destructive inflammatory response as opposed to the protective immune response. The association of controlled NETosis with the development of acute respiratory syndromes and chronic lung disorders [44] points to the possibility of the fact that the interaction of MIF-mediated neutrophil-macrophage interaction can play an important role in the severity of inflammatory processes in the lung tissues.

3.4 Dendritic Cells

The dendritic cells (DCs) potentially in the lung have a crucial role in the crossing of the innate and adaptive responses through their presence as an antigen-presenting cell. Antigens that are inhaled are captured by DCs and taken to the draining lymph nodes, where they promote naivety in T cells and rejuvenate their effector differentiation programs. They are strictly active in relation to the signaling embodied by the network of macrophages and local cytokines. Another example is the linkage of innate lymphoid cells with other activated macrophages, which further indicates the development of immune conditioning when mediated by DCs in specific situations in the 2 types of inflammatory settings [45]. MIF can be applied to a number of levels of DC biology. The microenvironmental cues can polarize T cells to adopt inflammatory or tolerogenic phenotypes by regulating DC maturation and producing cytokines by extracellular MIF in response to them. The effects of indirect activation of

macrophages as exerted by MIF during the priming of DCs can manifest with the dietary shifts in the cytokine signature of bacteria in allergic or fibrotic states dominated by type 2 immunity. This, on the other hand, may sustain the pro-inflammatory activation of DC by overstimulating the MIF signaling to result in increased tissue destruction by T cells. There must be balance in tolerance and immunity since the lung is exposed all the time to harmless antigens. Full-fledged DC-driven T cell priming during infection as well as chronic lung disease can be controlled by MIF due to its capacity to induce inflammatory signaling when interacting with the macrophage-ILC networks [45].

3.5 T Lymphocytes

The controllers of the adaptive immunological response within the lung are T cells, which, among them, CD4+ and CD8+ T cells have different functions, which are complementary to each other. Together with the delivery of the helper signals, the antigen-sensitive CD4+ T-lymphocytes are able to actively invite the monocytes and spearhead them into transformation into metabolically reactive and glycolytic macrophages with an augmented antimicrobial activity [46]. This indicates that a very strong relationship exists between the macrophage metabolic conditions and T cell activation, which can be influenced by MIF metabolism. MIF is able to modulate the CD4+ and CD8+ T cell response due to direct receptor interaction or indirect reprogramming of the macrophages and dendritic cells. MIF has the ability to lead to the polarization of Th1 and Th17 in the inflammatory status with the resultant production of interferon-γ and IL-17, respectively. Excessive polarization may lead to tissue pathology, but this may be advantageous to the clearing of the pathogens. Long-term maintenance of inflammatory signaling and the immunosuppressive effect of macrophages within the tumor environment may promote immune checkpoint resistance and prevent the effect of cytotoxic immunity in CD8+ lymphocytes. This can be achieved indirectly based on the fact that MIF controls the development of macrophages and production of cytokines to manage T cell fatigue and survival of effectors. As a result, MIF of pulmonary immunity should be seen as a more holistic immunoregulatory protein that does affect T cell arrival, differentiation, and metabolic balance functioning in both infections and cancer [46].

3.6 ILC2 and Innate Lymphoid Cells

Type 2 immunocytes, particularly innate lymphoid cells, are the primary actors of type 2 immunity in the lung. When the epithelial cells release alarmin, they promptly release IL-5 and IL-13, which induce eosinophilic inflammation and secretion of mucus and remodelling of the airways. The communications between the ILC2s and the alternatively activated macrophages develop a regulatory loop that determines the development of the lungs and the pathogenesis of chronic inflammatory disease [45]. MIF may influence ILC2 activity indirectly in this network, as it could have its effect as an upstream modulator of macrophage stimulation. It may be due to type 2 polarization of macrophage-created cytokines that leads to high levels of extracellular matrix and airway hyperresponsiveness of fibrotic lung disease and asthma. MIF might also affect the quality and maintenance of responses mediated by ILC2 by acting via the metabolic and inflammatory condition of macrophages. Further, the hypoxic and inflammatory microenvironment typical of the chronic pulmonary condition can be amplified to increase expression of MIF, which would promote interaction between macrophages and ILC. It implies that MIF may mediate it between the protective type 2 immunity and the remodelling of the pathogens. Since dysregulated innate immunity is a prerequisite of adaptive immunological involvement in asthma induced by allergies and fibrotic diseases, this interconnection is especially important to be aware of [45].

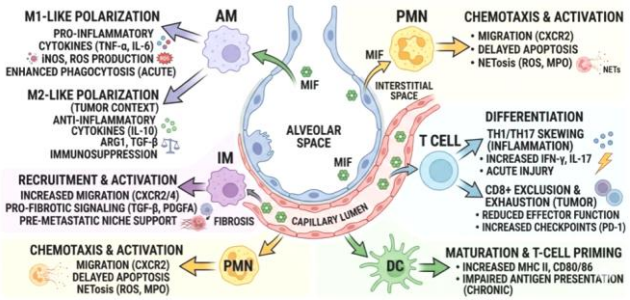

Figure 1: Cell-Specific Effects of MIF in the Lung Immune Compartment [47]

4. MIF IN PULMONARY INFECTIONS AND ACUTE INFLAMMATION

4.1 Bacterial Pneumonia

Severe bacterial pneumonia is a classic example of the state of dysregulated host inflammation that equally plays a role in the pathogenesis of the invasive pathogen. The potential outcomes of uncontrolled cytokine release in pneumococcal infections may lead to chronic sequelae of the lungs and acute destruction of organic structures in the implementation of a full-fledged inflammatory response [48]. In the provided

scenario, MIF may play a major role in actuating the application of cytokine storm-like responses. MIF may increase the injury of the alveoli by enhancing the recruitment of leukocytes and vascular disruption by further stimulating the production of TNF-alpha, IL-6, and other pro-inflammatory cytokines by the macrophages. It is also the overproduction of high nitric oxide (NO) and reactive oxygen species (ROS) that accompany cytokine magnification in bacterial pneumonia that is known as "antimicrobial defense." Even though the excess of ROS will result in the breakdown of epithelia and barrier destruction, the synthesis of NO by inducible nitric oxide synthase (iNOS) is important in clearing pathogens. Biasing the immune system towards tissue injury, MIF could be a mediator of tissue inflammatory signaling and the action of the macrophage that is required to trigger a shift between protective immunity and oxidative stress and iNOS. Therefore, it is probable that MIF is at the crossroads between immunopathology and antimicrobial defense in the case of bacterial pneumonia, and it further intensifies the inflammatory response, which otherwise triggers the body to acute lung injury and systemic effects [48].

4.2 Fungal Infections (Aspergillus, Pneumocystis)

Individuals who are immunodeficient or highly ill are more susceptible to fungi, including Aspergillus fumigatus and Pneumocystis species. The orchestrated innate immune signaling and macrophage activation contribute greatly towards host defense. Modifying the lipid mediator pathways, virulence factors secreted by the fungi, such as gliotoxin, can have a direct impact on innate immune responses and reduce the effectiveness of antimicrobial responses [49]. The immunomodulatory environment may be done in a twofold way that might be the work of MIF. On the one hand, the macrophages' activation with the help of MIF may help in fungus clearance by improving phagocytosis, cytokine secretion, and immune cells' recruitment. Decreased signaling in MIF may, however, augment the inflammatory destruction, and this may be greater in the small alveolar space in which gaseous exchange would be impaired by cellular inflammation and edema. More to the point, the lack of clearance is known to be actively engaged with the host immune signaling in order to avoid clearance by fungal infections. MIF is able to prevent or activate these evasion mechanisms according to the contexts in that it has the capability to alter the macrophage metabolic programming and inflammatory polarization. To facilitate this process, the role of fungal toxins in the regulation of lipid mediators in the MIF-dependent inflammatory pathways may also lead to the regulation of the macrophage reaction [49]. It is then expected that MIF will be a context-specific regulator of fungal lung infections, maintaining the possible threat of non-selective tissue damage and the antimicrobial activation.

4.3 Viral Infections (Influenza, SARS-CoV-2)

Examples of such factors include such viral respiratory diseases as influenza and SARS-CoV-2, which prove that the balance between immunopathology and antiviral immunity is a delicate phenomenon. Acute influenza infection triggers coordinated epithelial, macrophage, and endothelial stimulation, which determine the presence of strong cytokine production and tissue destruction as witnessed by detailed immunocompetent lung preparations [50]. MIF is in a good position to control the development of the disease in these inflammatory pathways. MIF would be beneficial in raising antiviral defense by conserving the survival of macrophages and encouraging cytokine-based invasion by cytotoxic cells. A constant increase in MIF, though, is a potential reason for the progressive amplification of cytokines as well as a contributor to the hyperinflammatory character of severe viral pneumonia. Type I and III interferon responses are especially represented by viral immunity. The load of interferon dysregulation has been identified as the pathophysiology of COVID-19 and severe influenza. MIF can disrupt interferon-mediated antiviral responses either by enhancing the impact of the inflammatory cascades or by disrupting the immune responses towards neither balanced control of viral fate, as it can modulate intercellular signaling pathways that are either linked to the NF-kB or to STAT activation. Therefore, MIF will most probably be functional as a molecular rheostat to viral lung infections, which is complemented with an early host defense and predisposes the disease to immunopathology with prolonged stimulation of the immune system [50].

4.4 Acute Lung Injury and ARDS

Regardless of the pathogenic viral agent, the final results of the acute pulmonary inflammation are acute lung injury (ALI) and acute respiratory disease syndrome (ARDS). The significant components of the pathophysiology of them are the activation of the macrophages and the transcriptional reprogramming of the inflammatory mediators. NF-κB p65 post-translational modification has developed

to be an obligatory regulator of inflammatory severity and macrophage polarization in ALI and has been discovered to monitor fresh molecular gateways in the course of the illness [51]. According to this theory, MIF can also be an upstream amplifier of transcriptional programs, and this requires NF-κB that is retained in the production of inflammatory cytokines. DAMPs stimulating activity of subsequent activating innate immune receptors and prolonging inflammation are also released along with tissue damage during the acute respiratory distress syndrome (ARDS). MIF may be produced under stressed or necrotic cells, possibly in conjunction with DAMP signaling, to cause additional dysfunctional endothelium and activate macrophages. On top of this, there is regulation of cell death mechanisms, including ferroptosis and pyroptosis, to facilitate cell death and propagation of the inflammation. This MIF-induced oxidative stress and inflammatory transcriptional circuit lytic cell death pathways have the potential to contribute to the damage of the alveoli. Consequently, MIF is an appropriate therapeutic target in acute pulmonary inflammation, as it is probably an interface of the intervention of DAMP-related activation, NF-kB signaling, and macrophage polarization as well as deleterious inflammatory cell death of ALI and ARDS [51].

Table 2: Role of MIF Across Major Pulmonary Infections and Acute Lung Syndromes [14]

Disease Category	Dominant Immune Cells	MIF Mechanistic Effect	Protective vs. Pathogenic	Therapeutic Evidence
Bacterial Pneumonia	Alveolar Macrophages	Upregulates TLR4; amplifies pro-inflammatory "burst"	**Pathogenic** (Excessive)	Anti-MIF reduces lung edema
Viral (COVID-19/Flu)	CD8+ T Cells / Monocytes	Drives "Cytokine Storm" via NLRP3 inflammasome	**Pathogenic** (Late stage)	Serum MIF correlates with ARDS
Fungal Infections	Neutrophils (PMNs)	Promotes Dectin-1 mediated phagocytosis/killing	**Protective** (Clearance)	MIF-deficiency increases mortality
Acute Lung Injury	Neutrophils	Activates CXCR2; inhibits PMN apoptosis	**Pathogenic**	ISO-1 improves alveolar barrier

5. MIF IN CHRONIC LUNG INFLAMMATION AND FIBROSIS

5.1 COPD and Airway Remodeling

COPD features include airway remodeling, which is chronic, and inborn immunity. The inflammation of the neutrophils, macrophages, and innate lymphoid cells accumulates in the airway wall and develops low-grade inflammation, which supports the tissue remodeling mechanism and epithelial cell damage [52]. In this case, MIF may be employed to enable the survival of innate immune cells with the stimulation of survival signaling and cytokine amplification. These pathways are chronic EGFR and STAT3 activations that have been linked to the hypersecretion of the mucus, cellular proliferation of the epithelial cells, and fibrotic thickening of the airways [52]. MIF is also prone to strengthening remodeling circuits because of an increased ability to strengthen inflammatory signaling as well as interaction with chains of transcriptional responses controlled by STAT3. Therefore, MIF may be a molecular connection between innovative structural changes of COPD airways and innate immune persistence triggered by growth factors.

5.2 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a disease that is marked by permanent inversion of the lung structure and accumulation of extracellular matrix (ECM) in the lung. The single pathogenic axis involves monocyte recruitment and contact of macrophage-fibroblast that activates fibroblasts and deposits collagen [53]. This essential importance of macrophage-specified remodelling is reflected by the experimental information that barring recruiting monocytes in conquering fibrotic advancement [53] through barring monocyte-macrophage recruiting action. MIF stimulation and maintenance of macrophage stimulation and chemotactic signaling could stimulate fibroblasts more and prolong the deposition of ECM. Besides, the transformation of fibroblasts into myofibroblasts could be done by the release of the mediators by the macrophages, and this causes the tissues to become hard. In this instance, MIF is also susceptible to playing a role in the empowerment of profibrotic-immune loops by connecting inflammatory persistence with the process of progressive functional loss and structure remodelling of IPF.

5.3 Hypoxia-Driven Fibroinflammatory Niches

Long-term generic inflammation and fibrosis of the lungs is commonly followed up by hypoxia of the region and normalizes hypoxia-inducible factors (HIFs) and reshapes the cellular metabolism. The HIF activity is also regulated in tumor biology and lung

disease development that is regulated by factor-inhibiting HIF (FIH) [54]. MIF has been established to have effects on hypoxia-responsive pathways, which can elevate downstream transcription of angiogenic and glycolytic genes and stabilization of HIF. Such a form of metabolic plasticity facilitates extracellular matrix remodeling, fibroblast survival, and macrophage survival in fibroinflammatory conditions. Therefore, MIF signaling can be used to facilitate metabolic cross-talk between stromal elements and immune cells through hypoxia. Next, presumably, MIF is involved in the maintenance of hypoxic and metabolically altered microenvironments that foster pathogenesis of fibrosis and unremitting inflammation [54].

6. MIF IN LUNG CANCER AND THE TUMOR IMMUNE MICROENVIRONMENT

6.1 MIF in Tumor Initiation and Metabolic Reprogramming

The origin and development of the tumor is referred to as "metabolic reprogramming." Cancer stem cells have the ability to secrete MIF to aid in immune evasion and glycolytic enhancement, and these create a protumorigenic environment [55]. MIF maintains inflammatory pathways that improve tumor development and anabolic proliferation and prefers aerobic glycolysis and network alterations of cytokines. Similarly, the common pathways can increase metabolic plasticity as well as safeguard cancerous cells in lung cancer against destruction by the immune system. In addition, MIF-specific metabolic signaling has the potential to affect adjacent immune cells to enforce macrophages to tumor-promoting states. In this regard, MIF is situated at the cross-section bridge of immunity and metabolism, and as a consequence, the development of tumors due to the creation of glycolysis regulation and maintenance of stem-like cell formations that are immune-insensitive occurs [55].

6.2 Tumor-Associated Macrophages (TAMs)

TAMs within lung tumors are a dominant immunological community; they often have the immunosuppressive M2-type behaviors. The tumors produce cytokines and metabolites that signal their differentiation to form circuits that provide inhibitory action to cytotoxic T cell responses and a pro-angiogenic action [56]. Some of the population types of macrophages have been attributed to the development of tumors and the failure to be absorbed by the immune response that includes ID1+ and TREM2 high populations [56]. MIF has the properties of augmenting TAM polarization that boosts survival signaling and enhances immunosuppressive transcriptional activities. MIF has the capability of enhancing macrophage-induced shutdown of effector cells, and these can be achieved by the means of augmenting the cytokines and chemokines. Hence, MIF will stabilize the tumor immunosuppressive network based on TAM in the tumor immune milieu, which allows the tumor to survive and metastasize [56].

6.3 Pre-metastatic Niche Formation in the Lung

EVs released by tumors precondition organs distant from the tumor cells' arrival at the lung, one of the frequent metastasis areas. EV-loaded mediators have the potential to find granulocytic myeloid-derived suppressor cells (gMDSCs) to alter the microenvironment to favor the seeding of the metastasis [57]. It is more a chemokine recruitment-based myeloid process and entails the following axes of chemokines: CXCL and CCL [57]. MIF is applicable with EV-derived signals in activating the gathering of myeloid cells and local immunosuppression because it can be applied as chemokine-like. Based on preserving inflammatory and metabolic reprogramming of recruited cells, MIF can enhance pre-metastatic niche extracellular matrix remodeling and vascular permeability. In this way, MIF is likely to enhance EV-governed myeloid immigration and stromal environment required to enable successful colonization of the lungs by metastasis [57].

6.4 MIF and Immune Checkpoint Resistance

In most cases, disease resistance to immunosuppressors such as anti-PD-1 therapy is linked with immunosuppressive development of the myeloid population and defective activation of the STAT3 signaling [58]. The inhibition of tumor cores by CD8 T cells and exclusion is involved in the recruitment of myeloid-derived suppressor cells (MDSCs) [58]. MIF has the ability to mediate these resistance responses by initiating the activation of adherent suppressive and STAT3 phenotypes of macrophages. Additional enhanced immune evasion is also provided by enamored PD-L1 expression, as well as the production of inflammatory cytokines. MIF is able to stabilize niches unfriendly to checkpoints by a rise of myeloid processes and hypothesizes the steady state of STAT3-dependent transcriptional systems. To counter the issue of PD-1 blockade resistance so as to reinstate the para-cytotoxic T cell infiltration in lung cancer, there is a chance of concentrating on the STAT317 May-MIF axis [58].

6.5 Engineered Macrophages and MIF Targeting

The generation of macrophages and targeting them towards the generation of MIF signaling have become increasingly popular treatment therapies. The random courses of cross-presentation have the potential of allowing higher numbers of phagocytic- and antigen-presenting-competent CAR-macrophages to stimulate T cells and overcome tumor heterogeneity [59]. It is also possible to perturb the tumor-supportive macrophage loops by also introducing MIF pathway inhibition drugs like ibudilast or small molecule drugs like ISO-1. In addition, CD74, which is the main receptor of MIF, inhibition would prevent the protumorigenic signaling in the immunological and cancer cells. In this way, a synaptic improvement in the antitumor immunology of MIF-targeted therapy and deactivation of immunosuppressive networks in combination with depressive macrophage therapy could be attained. This type of combinatorics can show that MIF is one of the nodes of the immune milieu of the lung tumor and that can be dealt with purposefully [59].

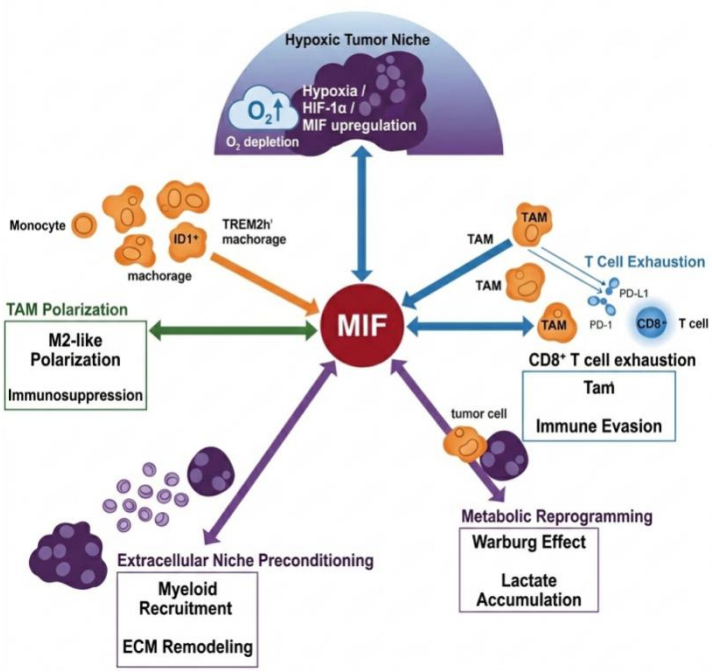

Figure 2 : MIF-Driven Remodeling of the Lung Tumor Immune Microenvironment [47]

Table 3: Therapeutic Strategies Targeting MIF Signaling in Lung Disease and Cancer [47]

Agent	Mechanism	Target Cell / Pathway	Disease Context	Status	Key Findings
Ibudilast (AV-411)	Allosteric MIF inhibitor	Macrophages / Tautomerase	ARDS, Asthma, Infection	Phase II / Repurposing	Attenuates cytokine storm and lung pathophysiology.
ISO-1	Small molecule inhibitor	Tautomerase active site	Sepsis, Lung Cancer	Preclinical	Inhibits tumor cell proliferation and TAM polarization.
Milatuzumab	Anti-CD74 monoclonal antibody	CD74 surface receptor	B-cell malignancies, NSCLC	Clinical trials	Blocks MIF-induced survival signaling in tumor cells.
SCD-19	MIF antagonist	MIF-CD74 interaction	Acute Lung Injury (ALI)	Preclinical	Reduces alveolar neutrophil infiltration and pulmonary edema.

7. SYSTEMS-LEVEL INTEGRATION: MIF AS AN IMMUNOMETABOLIC RHEOSTAT

It is possible to regard MIF as an immunometabolic rheostat and the one that integrates the infection, inflammation, and cancer continuum in the lung. MIF boosts the maximal innate immunity reaction in an effort to assist in the clearance of pathogens in the era of contemporaneous contagion, yet at chronic stages, it may restructure protumorigenically and induce the emergence of chronic inflammation. This means that MIF is a context-dependent signal modulator/regulator according to microenvironment. It also disrupts immunometabolic checkpoints, to which glycolytic reprogramming, polarization of the macrophagic, and inflammatory signaling converge.

An increase in gut-lung immunometabolic interaction happens in the conditions of pathogenic and immune-regulating dysbiosis of microbes and breakdown of systemic inflammatory responses of the pulmonary immune system [61]. Also, stressors, including hypoxia and prolonged psychological stresses that mutilate metabolism and inflammatory cascades still further, assist the immune rebalancing of distal body systems by MIF [61].

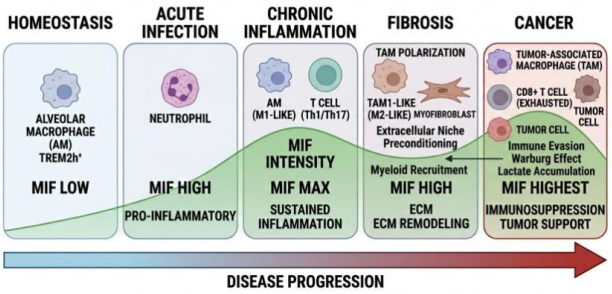

Figure 3: Conceptual Model: MIF as a Context-Dependent Regulator of Lung Immunocompetence Across the Disease Spectrum [47]

8. CLINICAL TRANSLATION AND THERAPEUTIC PERSPECTIVES

Circulating MIF is also reported to be diagnostically relevant in some infectious diseases, thus making it a desirable biomarker of intoxication with the specific disease at an extremely early phase of inflammation [63]. A combination of serum MIF should be used to diagnose pulmonary diseases as a complementary measure to classify individuals that are at risk of immunotherapy resistance or hyperinflammatory development. The combination of the MIF targeting and next-generation immunotherapies would help to improve the results of the treatment in the situation of lung cancer when the immune regulation is crucial, and the immune system is instrumental [64]. The use of the MIF pathway blockers with the checkpoint inhibitors as combination therapy can be used with different ways of individualized medicine, where treatment depends on immune-metabolic characteristics of the specific patient. Systemic MIF inhibition, however, is also able to compromise host defense and tissue repair; therefore, the safety concern is of utmost consideration [63, 64].

9. UNRESOLVED QUESTIONS AND FUTURE DIRECTIONS

MIF in diseased lungs suppressed has vastly considerable information missing concerning the geographical and the cellular provenance. The one-cell MIF-producing populations undergoing a complex microenvironment are given a chance to be resolved with the use of the immune system-on-chip biofabrication designs and spatial transcriptomics [65]. The other unresolved problem is the functional redundancy of MIF and its homolog D-DT, specifically during tumor and chronic inflammatory states. The importance of the contextual inhibitory means can be extremely higher than that of the global blocking. Immune-competent organoid and lung-on-a-chip systems are state-of-the-art systems providing more physiologically relevant systems to address both MIF-dependent circuits and to apply a set of targeted therapies in controlled conditions using human-phenotype programs [66].

10. CONCLUSION

MIF is a convergent molecular node, and this connects the gap between lung cancer and fibrosis and chronic inflammation to acute immune activation. Compared with being a mere pro-inflammatory cytokine, MIF is a versatile context-sensitive regulator that considers the hypoxia, the metabolic rewiring, and immune cell plasticity. There is also a concerted effort between T lymphocytes and neutrophils and macrophages and dendritic cells in the pathogenic remodelling and the preventative host defense by MIF. It develops pre-metastatic niches, has immune checkpoint resistance properties, and polarizes tumor macrophages, the latter of which is of relevance in therapy. Urgently, novel information regarding systems-level uncovers that MIF is an immunometabolic rheostat in the complicated microenvironment of the lungs. Even in cases when MIF therapeutic targeting becomes a necessity, such precision techniques that take into account the cell environment and stage of the disease would be vital, despite the fact that both the consideration of cell environment and disease stage would be crucial. Applications of the organoid platforms and spatial transcriptomics would allow us to actualize our knowledge and hasten the procedure of producing tailored and specific pulmonary-based treatment in the future.

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