





Review

# The Role of Macrophages in Connective Tissue Disease-Associated Interstitial Lung Disease: Focusing on Molecular Mechanisms and Potential Treatment Strategies

Chia-Chun Tseng<sup>1,2,3</sup>, Ya-Wen Sung<sup>4</sup>, Kuan-Yu Chen<sup>3</sup>, Pin-Yi Wang<sup>3</sup>, Chang-Yi Yen<sup>3</sup>, Wan-Yu Sung<sup>3</sup>, Cheng-Chin Wu<sup>3</sup>, Tsan-Teng Ou<sup>3</sup>, Wen-Chan Tsai<sup>3</sup>, Wei-Ting Liao<sup>5,6,\*</sup> , Chung-Jen Chen<sup>7</sup>, Su-Chen Lee<sup>8</sup>, Shun-Jen Chang<sup>9</sup> and Jeng-Hsien Yen<sup>1,3,10,\*</sup> 

- <sup>1</sup> Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan
  - <sup>2</sup> School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan
  - <sup>3</sup> Division of Rheumatology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
  - <sup>4</sup> Department of Nursing, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
  - <sup>5</sup> Department of Biotechnology, College of Life Science, Kaohsiung Medical University, Kaohsiung 807, Taiwan
  - <sup>6</sup> Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
  - <sup>7</sup> Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung 801, Taiwan
  - <sup>8</sup> Laboratory Diagnosis of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan
  - <sup>9</sup> Department of Kinesiology, Health and Leisure Studies, National University of Kaohsiung, Kaohsiung 811, Taiwan
  - <sup>10</sup> Institute of Biomedical Sciences, National Sun Yat-Sen University, Kaohsiung 804, Taiwan
- \* Correspondence: wtliao@kmu.edu.tw (W.-T.L.); jehsye@kmu.edu.tw (J.-H.Y.);  
Tel.: +886-7-3121101 (ext. 2791) (W.-T.L.); +886-7-3121101 (J.-H.Y.); Fax: +886-7-3125339 (W.-T.L.); +886-7-3221505 (J.-H.Y.)



**Citation:** Tseng, C.-C.; Sung, Y.-W.; Chen, K.-Y.; Wang, P.-Y.; Yen, C.-Y.; Sung, W.-Y.; Wu, C.-C.; Ou, T.-T.; Tsai, W.-C.; Liao, W.-T.; et al. The Role of Macrophages in Connective Tissue Disease-Associated Interstitial Lung Disease: Focusing on Molecular Mechanisms and Potential Treatment Strategies. *Int. J. Mol. Sci.* **2023**, *24*, 11995. <https://doi.org/10.3390/ijms241511995>

Academic Editor: Alexander Schramm

Received: 20 April 2023

Revised: 24 July 2023

Accepted: 25 July 2023

Published: 26 July 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

**Abstract:** Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a severe manifestation of CTD that leads to significant morbidity and mortality. Clinically, ILD can occur in diverse CTDs. Pathologically, CTD-ILD is characterized by various histologic patterns, such as nonspecific interstitial pneumonia, organizing pneumonia, and usual interstitial pneumonia. Abnormal immune system responses have traditionally been instrumental in its pathophysiology, and various changes in immune cells have been described, especially in macrophages. This article first briefly overviews the epidemiology, clinical characteristics, impacts, and histopathologic changes associated with CTD-ILD. Next, it summarizes the roles of various signaling pathways in macrophages or products of macrophages in ILD, helped by insights gained from animal models. In the following sections, this review returns to studies of macrophages in CTD-ILD in humans for an overall picture of the current understanding. Finally, we direct attention to potential therapies targeting macrophages in CTD-ILD in investigation or in clinical trials, as well as the future directions regarding macrophages in the context of CTD-ILD. Although the field of macrophages in CTD-ILD is still in its infancy, several lines of evidence suggest the potential of this area.

**Keywords:** connective tissue disease; interstitial lung disease; macrophage; systemic sclerosis

## 1. Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of multiple entities characterized by damage to the lung parenchyma due to varying degrees of inflammation and fibrosis [1]. ILDs arise from a broad spectrum of known or unknown etiologies and inflict a substantial burden on patients and health care systems [2]. Connective tissue disease (CTD), also known as collagen vascular disease [3], is a common cause associated with ILD [4], with 15% of ILDs arising from CTD [5]. CTD includes several disease entities,

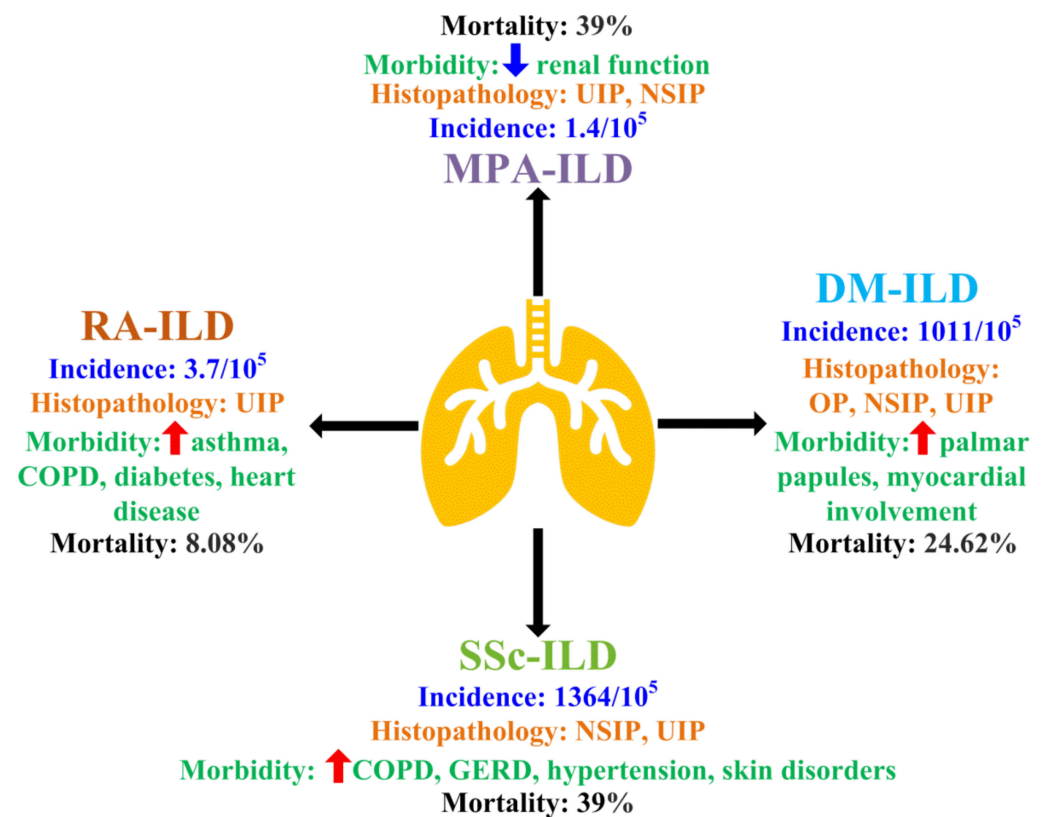
such as dermatomyositis (DM), microscopic polyangiitis (MPA), rheumatoid arthritis (RA), and systemic sclerosis (SSc). Corresponding to CTD-associated ILDs (CTD-ILDs) are DM-associated ILD (DM-ILD), MPA-associated ILD (MPA-ILD), RA-associated ILD (RA-ILD), and SSc-associated ILD (SSc-ILD). Pathologically, CTD-ILD can be classified based on respective histopathologic patterns, including nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and usual interstitial pneumonia (UIP) [6]. In practice, CTD-ILD is usually diagnosed through multidisciplinary discussion (MDD) including review of the clinical features, imaging, serology, and pathology by pulmonologists, radiologists, rheumatologists, and pathologists [7].

Clinically, different CTD-ILDs have distinct epidemiologies, pathologic changes, comorbidities, and prognoses (Figure 1). The incidence of DM-ILD is  $1011/10^5$  [8]; it is characterized by OP, NSIP, and UIP [9] and associated with palmar papules and myocardial involvement [10,11], and its mortality rate is as high as 24.62% [12]. The estimated incidence of MPA-ILD is  $1.4/10^5$  [13]; it is characterized by UIP and NSIP [14] and associated with decreased renal function [15], and its mortality rate is up to 39% [16]. The estimated incidence of RA-ILD is  $3.7/10^5$  [17]; it is presented as UIP [18] and associated with increased asthma, chronic obstructive pulmonary disease (COPD), diabetes, and heart disease [19,20], and its mortality rate is 8.08% [17]. The incidence of SSc-ILD is  $1364/10^5$  [21]; it is characterized by NSIP and UIP [14] and is associated with COPD, gastroesophageal reflux disease (GERD), hypertension, and skin disorders [22], and it has high mortality rate (39%) [23]. Overall, in CTD, the presence of ILD could lead to increased morbidity and mortality [24].

Although the mechanisms contributing to ILD in the context of CTDs are not known in detail, the prevailing hypothesis suggests the involvement of abnormal inflammation and subsequent exaggerated fibrotic reactions [1]. Interestingly, macrophages not only coordinate inflammation process but also mediate the formation of fibrosis. Given these characteristics of macrophages, it makes sense that macrophages play critical roles in the pathogenesis of CTD-ILD. The roles of macrophages have been suggested in numerous studies. For example, macrophages in the lungs of SSc-ILD upregulated profibrotic factors that promoted lung fibroblast activation [25]. Another example is DM-ILD. Previous studies reported that ferritin was produced by macrophages [26] and correlated with lung function parameters and survival [27]. IL-18 was also secreted by macrophages [28], elevated in DM-ILD compared with DM without ILD [29], and correlated with the severity of pulmonary disease [30]. Together, these studies point to the importance of macrophages in the development and progression of CTD-ILD.

Macrophages are versatile cells that exhibit high plasticity according to crosstalk between macrophages and the tissue microenvironment. Historically, analogous to the Th1/Th2 dichotomy, studies have characterized macrophages as classically activated (M1) or alternatively activated (M2) according to the activation status. Although the dichotomous inflammatory M1/repair M2 model cannot fully represent the current understanding of macrophage biology in ILD, studies on fibrosis usually build upon this classification scheme. As one of the most versatile cell types with diverse immunity functions, macrophages not only initiate an inflammatory response after injury but are also involved in the injury resolution and repair. In other words, in the airway and lung microenvironment, macrophages orchestrate the development and establishment of ILD. In this process, macrophage products and/or macrophages themselves are implicated at each key step. Work utilizing ILD patient samples provided several pieces of evidence of altered macrophages in ILD, whose functional importance was further confirmed in murine models [31].

Radiologically, CTD-ILD is characterized by various patterns of fibrosis using high-resolution computed tomography (HRCT) in the lung bases of patients with CTD, such as RA and SSc [32]. Most of our understanding of CTD-ILD comes from studies on pulmonary fibrosis (PF) in animal models. Therefore, we will first review the current knowledge of macrophages in the ILD/PF of animal models and then review recent advances in the molecular biology of CTD-ILD in the literature.



**Figure 1.** Incidence, histopathology features, morbidities, and mortalities of individual CTD-ILD discussed in this review. The figure summarizes incidence, histopathology features, morbidities, and mortalities of CTD-ILD discussed in this review. (1) The incidence of DM-ILD is  $1011/10^5$ . Histopathological changes associated with DM-ILD are organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), and usual interstitial pneumonia (UIP). Patients have increased palmar papules and myocardial involvement, with mortality rate of up to 24.62%. (2) The incidence of MPA-ILD is around  $1.4/10^5$ . The pathological patterns are often UIP and NSIP. It is associated with decreased renal function and has a mortality rate of up to 39%. (3) The estimated incidence of RA-ILD is  $3.7/10^5$ . It is characterized by UIP. The patients usually suffer from increased asthma, chronic obstructive pulmonary disease (COPD), diabetes, and heart disease, and the mortality rate is 8.08%. (4) The incidence of SSc-ILD is  $1364/10^5$ . It is characterized by NSIP and UIP, accompanied by COPD, gastroesophageal reflux disease (GERD), hypertension, and skin disorders and a mortality rate of about 39%. Red arrow—increase; blue arrow—decrease.

## 2. Roles of Signaling Pathways of Macrophages in ILD/PF in Animal Models

Regarding the relationship between macrophages and PF, several studies support the vital roles of macrophages in the pathogenesis of lung fibrosis. Macrophages in lung tissue samples from patients with fibrosis are higher compared to controls without fibrosis [33]. Macrophages play a mechanistic role in exacerbating lung fibrosis [34]. On the other hand, the ablation of macrophages was shown to significantly decrease fibroblasts and collagen deposition, ameliorating lung fibrosis [35]. Macrophages participate in both the inflammation and tissue repair phases of PF through various mechanisms, as detailed below.

(1) Caspase pathway: Studies show that MCU in PF macrophages leads to augmented expression of carnitine palmitoyltransferase 1A (CPT1A). By inducing Bcl-2 expression, CPT1A decreases caspase-3 activity, which attenuates macrophage apoptosis and thereby facilitates lung fibrosis progression (Table 1). The deletion of Bcl-2 in macrophages protects mice from developing PF [36].

(2) CCR2 axis: The CCL2/CCR2 axis is a major regulator of monocyte trafficking and plays an essential role in PF. CCR2 deficiency suppresses macrophage infiltration

and reduces macrophage-derived MMP-2 and MMP-9 production, which decreases lung extracellular matrix content in the lungs (Table 1) and protects mice from PF [37].

(3) CCR4 axis: CCR4 promotes tissue injury through the induction of the M1 macrophage phenotype. In the absence of CCR4, macrophages upregulate the scavenging receptor D6, which attenuates inflammation and tissue injury (Table 1) and protects mice from lung fibrosis [38].

(4) CD204 axis: Collagen type I monomers stimulate macrophages to induce CD204 expression. In the context of elevated CD204, PF macrophages show hyperreactivity to stimulation with collagen type I monomers, resulting in exacerbated CCL18 secretion [39]. CCL18 triggers collagen production by fibroblasts. However, through  $\beta_2$ -integrins and scavenger receptors, macrophages in the vicinity bind to collagen type I and increase CCL18 production. These reactions generate a feed-forward loop of augmented, ceaseless macrophage activation and unrestricted collagen production by fibroblasts (Table 1) [40].

(5) Glycolysis: Macrophages from fibrotic lungs assume the elevated expression of the glucose transporter GLUT1 [41], which augments the glycolysis required for the profibrotic profile in macrophages from fibrotic lungs (Table 1) [42].

(6) GSK pathway: TRIB3 is significantly upregulated in the macrophages of patients with PF. The TRIB3-GSK-3 $\beta$  interaction inhibits A20 activity and stabilizes C/EBP $\beta$  to induce macrophage activation, which triggers the transformation of lung fibroblasts into myofibroblasts, driving lung fibrosis (Table 1). Consequently, the macrophage-specific knockout of *TRIB3* suppresses fibrotic changes in the lungs [43].

(7) HIF pathway: Macrophages of fibrotic lungs show increased HIF1A, which upregulates the ADORA2B receptor on macrophages. ADORA2B contributes to macrophage differentiation and the production of profibrotic mediators (Table 1), facilitating fibrosis in the lung [44].

(8) Itaconate axis: In the murine PF model, aconitate decarboxylase 1 (*ACOD1*) decarboxylates cis-aconitate to itaconate, and itaconate suppresses fibroblast proliferation and profibrotic activity, thereby limiting the severity of PF (Table 1). *ACOD1* deficiency in macrophages induces profibrotic gene expression and worsens lung fibrosis [45].

(9) Macrophage migration: In the process of lung fibrosis, macrophages migrate into or within the lung to orchestrate and amplify fibrosis. In humans, monocyte migration is enhanced in PF. *PLXNC1* is underexpressed and *Syt7* is overexpressed in PF, and *PLXNC1* suppresses *Syt7*-driven macrophage migration (Table 1). The underexpression or absence of *PLXNC1* exacerbates macrophage migration and aggravates experimentally induced lung fibrosis. Conversely, restoring *PLXNC1* in macrophages is sufficient to attenuate fibrosis [46].

(10) MAPK signaling: Human fibrotic lung exhibits augmented *FOXM1* expression in macrophages. *FOXM1* activates *DUSP1* and inhibits the p38 MAPK signaling, therefore ameliorating lung fibrosis (Table 1). In agreement with this, macrophage-specific *FOXM1* knockout mice develop severe PF. On the other hand, the transfer of *FOXM1*-expressing monocytes protects *FOXM1*-deficient mice against lung fibrosis [47].

(11) STAT6 signaling: Cu,Zn-superoxide dismutase (Cu,Zn-SOD) is expressed in macrophages [48]. Cu,Zn-SOD-mediated H<sub>2</sub>O<sub>2</sub> generation activates STAT6 (Table 1) [49]. In the same way, macrophages isolated from fibrotic lungs have elevated *Gab2*, which increases STAT6 activation (Table 1) [50]. *SART1* in macrophages facilitates the STAT6 signaling axis (Table 1) [51]. *S1PR2* increases STAT6 activation (Table 1) [52]. These changes all accelerate STAT6 signaling and subsequent M2 polarization, triggering the development of PF [49–52].

(12) TGF- $\beta$  signaling: There are several ways to modulate macrophage TGF- $\beta$  signaling in PF. For example, Akt-mediated reactive oxygen species (ROS) production induces mitophagy and contributes to macrophage apoptosis resistance, which results in upregulated transforming growth factor- $\beta$  (TGF- $\beta$ ) [53]. Similarly, C/EBP homologous protein (CHOP) decreases the expression of *SOCS1* and *SOCS3*, thereby enhancing STAT6/PPAR $\gamma$  signaling, which is essential for TGF- $\beta$  production (Table 1) [54]. Another example is *MBD2*.

MBD2 selectively binds to the *SH2-containing inositol 5'-phosphatase (SHIP)* promoter in macrophages, by which MBD2 represses *SHIP* expression and enhances PI3K/Akt signaling to promote the macrophage M2 program and the production of downstream TGF- $\beta$  [55]. In the same way, *FBXW7* is an E3 ubiquitin ligase, whose expression in the macrophages of pulmonary tissue fibrosis mice is markedly decreased, and the deficiency of macrophage *FBXW7* promotes the recruitment and accumulation of phagocytes, increases the K48-linked polyubiquitination and proteasome degradation of c-Jun, and downregulates the expression of TGF- $\beta$  (Table 1) [56]. When TGF- $\beta$  is increased through these pathways, enhanced fibroblast differentiation and fibrosis ensues [53].

(13) TNF pathway: STAT1 is expressed in lung macrophages [57]. STAT1 induces ICAM-1 and downstream TNF from macrophages and the subsequent infiltration of inflammatory cells and eventual fibrosis (Table 1) [58]. In agreement with this, STAT1 inhibition ameliorates collagen deposition in the lungs in an animal model [59]. In the same way, CD300c2 enhances high-mobility group box protein-1 (HMGB-1)-induced macrophage activation to produce tumor necrosis factor (TNF), which is a leukocyte chemoattractants, resulting in the accumulation of augmented immune cells, inflammation, and the aggravation of lung fibrosis (Table 1) [60].

**Table 1.** Signaling pathways of macrophages in ILD/PF in animal models. “ $\rightarrow$ ”—lead to, “ $\downarrow$ ”—decrease, “ $\uparrow$ ”—increase.

| Signaling Pathways   | Results   | Reference |
|--|---|-----------|
| Caspase pathway  |   |           |
| MCU $\uparrow$ CPT1A $\rightarrow$ $\uparrow$ Bcl-2 $\rightarrow$ $\downarrow$ caspase-3 activity  | $\downarrow$ macrophage apoptosis<br>$\rightarrow$ $\uparrow$ fibrosis                          | [36]      |
| CCR2 axis  |   |           |
| CCR2 $\uparrow$ macrophage infiltration $\rightarrow$ $\uparrow$ MMP-2/MMP-9   | $\uparrow$ extracellular matrix deposition  | [37]      |
| CCR4 axis  |   |           |
| CCR4 $\uparrow$ inflammation and tissue injury   | $\uparrow$ fibrosis   | [38]      |
| CD204 axis   |   |           |
| collagen type I monomers $\uparrow$ CD204  | $\uparrow$ CCL18 $\rightarrow$ $\uparrow$ collagen production<br>$\rightarrow$ $\uparrow$ CCL18 | [39,40]   |
| Glycolysis   |   |           |
| GLUT1 $\uparrow$ glycolysis  | $\uparrow$ profibrotic macrophages  | [42]      |
| GSK pathway  |   |           |
| TRIB3-GSK-3 $\beta$ interaction $\downarrow$ A20 activity and stabilizes C/EBP $\beta$ $\rightarrow$ macrophage activation                               | $\uparrow$ fibroblasts transform to myofibroblasts  | [43]      |
| HIF pathway  |   |           |
| HIF1A $\uparrow$ ADORA2B $\rightarrow$ $\uparrow$ macrophage differentiation   | $\uparrow$ profibrotic mediators  | [44]      |
| Itaconate axis   |   |           |
| ACOD1 $\rightarrow$ $\uparrow$ itaconate   | $\downarrow$ fibroblast proliferation and profibrotic activity                                  | [45]      |
| Macrophage migration   |   |           |
| PLXNC1   | $\downarrow$ macrophage migration   | [46]      |
| MAPK signaling   |   |           |
| FOXO1 activates DUSP1 $\rightarrow$ $\downarrow$ p38 MAPK signaling  | $\downarrow$ fibrosis   | [47]      |
| STAT6 signaling  |   |           |
| Cu,Zn-SOD $\uparrow$ H <sub>2</sub> O <sub>2</sub> $\rightarrow$ activates STAT6   | $\uparrow$ M2 polarization  | [49]      |
| Gab2 $\rightarrow$ activates STAT6   |   | [50]      |
| SART1 $\rightarrow$ $\uparrow$ activates STAT6   |   | [51]      |
| S1PR2 $\rightarrow$ $\uparrow$ activates STAT6   |   | [52]      |
| TGF- $\beta$ signaling   |   |           |
| Akt $\uparrow$ ROS $\rightarrow$ $\uparrow$ mitophagy $\uparrow$ apoptosis resistance $\rightarrow$ $\uparrow$ TGF- $\beta$                              | $\uparrow$ fibroblast differentiation   | [53]      |
| CHOP $\downarrow$ SOCS1/SOCS3 $\rightarrow$ $\uparrow$ STAT6/PPAR $\gamma$ signaling $\rightarrow$ $\uparrow$ TGF- $\beta$                               |   | [54]      |
| MBD2 $\downarrow$ <i>SHIP</i> $\rightarrow$ $\uparrow$ PI3K/Akt signaling $\rightarrow$ $\uparrow$ M2 polarization $\rightarrow$ $\uparrow$ TGF- $\beta$ |   | [55]      |
| <i>FBXW7</i> $\downarrow$ phagocyte recruitment $\uparrow$ c-Jun degradation $\rightarrow$ $\downarrow$ TGF- $\beta$                                     |   | [56]      |
| TNF pathway  |   |           |
| STAT1 $\rightarrow$ $\uparrow$ ICAM-1 $\rightarrow$ $\uparrow$ TNF   | $\uparrow$ inflammatory cells infiltration  | [58,59]   |
| CD300c2 $\rightarrow$ $\uparrow$ macrophage activation $\rightarrow$ $\uparrow$ TNF  | $\rightarrow$ $\uparrow$ fibrosis   | [60]      |



### 3. Roles of Macrophage-Derived Secretory Proteins/microRNAs in ILD/PF in Animal Models

In addition to macrophages themselves, macrophage-derived secretory proteins and microRNAs also execute various biological functions to modulate the lung fibrotic process.

#### 3.1. Macrophage-Derived Secretory Proteins/microRNAs That Aggravate ILD/PF in Animal Models

(1) ADAM17: ADAM17 in association with membrane-bound IL-6R $\alpha$  (mIL-6R $\alpha$ ) is increased in macrophages in fibrotic lungs. ADAM17 promotes the shedding of mIL-6R $\alpha$  from the membranes of activated macrophages, thereby initiating IL-6 trans-signaling. IL-6 trans-signaling enhances fibroblast proliferation and extracellular matrix (ECM) production (Table 2) and the neutralization of IL-6 trans-signaling attenuates PF [61].

(2) AT1R: Macrophages secrete a considerable number of exosomes bearing AT1R, which are taken up by fibroblasts and result in higher levels of AT1R, the activation of the profibrotic TGF- $\beta$ /Smad2/Smad3 pathway, the production of  $\alpha$ -collagen I, and augmented Ang II secretion by fibroblasts. Interestingly, Ang II increases the number of macrophage exosomes and AT1R secretion, leading to a positive feedback between Ang II and exosome production involved in lung fibrosis (Table 2) [62].

(3) CCL6: CCL6, also called C10, is expressed in the macrophages and also attracts macrophages. Upregulated CCL6 accounts for the increased susceptibility to PF in the mice model. The neutralization of CCL6 attenuates subsequent lung fibrosis (Table 2) [63].

(4) Fibronectin: Compared to normal macrophages, PF macrophages produce more fibronectin [64]. Fibronectin transform fibroblasts to myofibroblasts, which lead to a local accumulation of extracellular matrix and hence the development of fibrosis in the lungs (Table 2) [65].

(5) Galectin-3: Galectin-3 is produced by macrophages and the levels of galectin-3 in CTD-ILD patients are higher than in control patients. Galectin-3 induces the production of TNF- $\alpha$  in macrophages, and galectin-3 expression in macrophages is also induced by TNF- $\alpha$ , creating a self-perpetuating cycle between TNF- $\alpha$  and galectin-3 to support inflammation. In addition, galectin-3 stimulates fibroblasts to induce proliferation (Table 2). All these changes promote lung fibrosis [66].

(6) IGF-I: Macrophages secrete IGF-I, which is increased in PF patients. Macrophage-derived IGF-I activates the prosurvival kinase Akt, which protects myofibroblasts from apoptosis, contributing to fibrosis (Table 2) [67]. Correspondingly, decreasing IGF-I ameliorates the severity of lung fibrosis [37].

(7) IL-1 $\beta$ : IL-1 $\beta$  induces inflammation with leukocyte influx and upregulates myofibroblast differentiation, resulting in augmented pulmonary collagen deposition (Table 2) and lung fibrosis [68,69].

(8) MIP-1 $\alpha$ : Macrophages secrete MIP-1 $\alpha$ , which promotes leukocyte accumulation [70]. On the contrary, anti-MIP-1 $\alpha$  antibodies significantly reduce pulmonary mononuclear phagocyte accumulation and ensue fibrosis (Table 2) [37].

(9) miR-328: Macrophage-derived miR-328 inhibits the family with sequence similarity 13 member A (FAM13A). This induces lung fibroblast proliferation and the overexpression of collagen 1A, collagen 3A, and alpha-smooth muscle actin ( $\alpha$ -SMA), which aggravate fibrosis (Table 2) [71]. On the other hand, silencing miR-328 in M2 macrophages alleviates the progression of lung tissue fibrosis [72].

(10) NTN1: NTN1<sup>+</sup> macrophages also accumulate in fibrotic lungs. Through interaction with DCC, macrophage-derived NTN1 impacts adrenergic nerve remodeling, which is required for lung fibrosis (Table 2) [73].

(11) PDGF: Macrophages from animal models of PF secrete PDGF, which is a potent mitogen for fibroblasts, facilitating lung fibrosis (Table 2) [74].

(12) S100A4: M2-polarized macrophages secrete S100A4, which stimulates the proliferation and activation of fibroblasts and is increased in PF (Table 2). The inhibition of S100A4 reduces histological evidence of lung fibrosis [75].

(13) TGF- $\beta$ : In the PF model, macrophages secrete TGF- $\beta$  [76]. TGF- $\beta$  increases PAI-1 expression in macrophages via Smad3, leading to extracellular stroma accumulation. These abnormalities favor lung fibrosis [77].

(14) Wnt: Wnt expression is noted in macrophages [78]. Wnt/ $\beta$ -catenin signaling promotes the differentiation of infiltrated monocyte-macrophage populations that contribute to lung fibrosis (Table 2). Therefore, the loss of the Wnt coreceptor low density lipoprotein receptor-related protein 5 (LRP5) attenuates the lung fibrotic process [79].

**Table 2.** Macrophage-derived secretory proteins/microRNAs in ILD/PF in animal models. “ $\rightarrow$ ”—lead to, “ $\downarrow$ ”—decrease, “ $\uparrow$ ”—increase.

| Molecules  | Characteristics | Signaling Pathway  | Reference |
|--|-----------------|--|-----------|
| Macrophage-derived secretory proteins/microRNAs that aggravate ILD/PF  |                 |  |           |
| ADAM17   | Protein         | $\uparrow$ shedding of mIL-6R $\alpha$ $\rightarrow$ $\uparrow$ IL-6 trans-signaling $\rightarrow$ $\uparrow$ fibroblast proliferation and ECM production  | [61]      |
| AT1R   | Protein         | AT1R taken up by fibroblasts $\rightarrow$ $\uparrow$ profibrotic production, $\uparrow$ TGF- $\beta$ /Smad2/Smad3 pathway, $\uparrow$ $\alpha$ -collagen I production, $\uparrow$ Ang II secretion by fibroblasts $\rightarrow$ $\uparrow$ macrophage exosomes and AT1R in exosomes | [62]      |
| CCL6   | Protein         | $\uparrow$ fibrosis  | [63]      |
| Fibronectin  | Protein         | $\uparrow$ myofibroblasts $\rightarrow$ $\uparrow$ extracellular matrix deposition   | [64,65]   |
| Galectin-3   | Protein         | $\uparrow$ TNF- $\alpha$ $\rightarrow$ $\uparrow$ galectin-3 $\rightarrow$ $\uparrow$ inflammation, $\uparrow$ fibroblast proliferation  | [66]      |
| IGF-I  | Protein         | activates Akt $\rightarrow$ $\downarrow$ myofibroblast apoptosis   | [67]      |
| IL-1 $\beta$   | Protein         | $\uparrow$ leukocyte influx, $\uparrow$ myofibroblasts $\rightarrow$ $\uparrow$ collagen deposition  | [68,69]   |
| MIP-1 $\alpha$   | Protein         | $\uparrow$ leukocyte accumulation $\rightarrow$ $\uparrow$ fibrosis  | [37,70]   |
| miR-328  | microRNA        | $\downarrow$ FAM13A $\rightarrow$ $\uparrow$ fibroblast proliferation and $\uparrow$ collagen 1A, $\uparrow$ collagen 3A, $\uparrow$ $\alpha$ -SMA   | [71]      |
| NTN1   | Protein         | interacts with DCC $\rightarrow$ impacts adrenergic nerve remodeling $\rightarrow$ $\uparrow$ fibrosis   | [73]      |
| PDGF   | Protein         | a mitogen for fibroblasts  | [74]      |
| S100A4   | Protein         | $\uparrow$ fibroblast proliferation and activation   | [75]      |
| TGF- $\beta$   | Protein         | $\uparrow$ PAI-1 $\rightarrow$ $\uparrow$ extracellular matrix   | [77]      |
| Wnt  | Protein         | $\uparrow$ differentiation of monocyte-macrophage $\rightarrow$ $\uparrow$ fibrosis  | [79]      |
| Macrophage-derived secretory proteins/microRNAs that ameliorate ILD/PF |                 |  |           |
| Pentraxin-2 (serum amyloid P) [80]                                     | Protein         | $\downarrow$ M2 differentiation  | [81]      |
| miR-142-3p   | microRNA        | $\downarrow$ TGF $\beta$ -R1 $\rightarrow$ $\downarrow$ profibrotic genes  | [82]      |

### 3.2. Macrophage-Derived Secretory Proteins/microRNAs That Ameliorate ILD/PF in Animal Models

(1) Pentraxin-2: Pentraxin-2, also called serum amyloid P (SAP) [80], reduces M2 differentiation and subsequent TGF- $\beta$ -mediated lung fibrosis (Table 2) [81].

(2) miR-142-3p: Macrophages secrete antifibrotic miR-142-3p, which reduces the expression of transforming growth factor  $\beta$  receptor 1 (TGF $\beta$ -R1) and downstream profibrotic genes in PF (Table 2) [82].

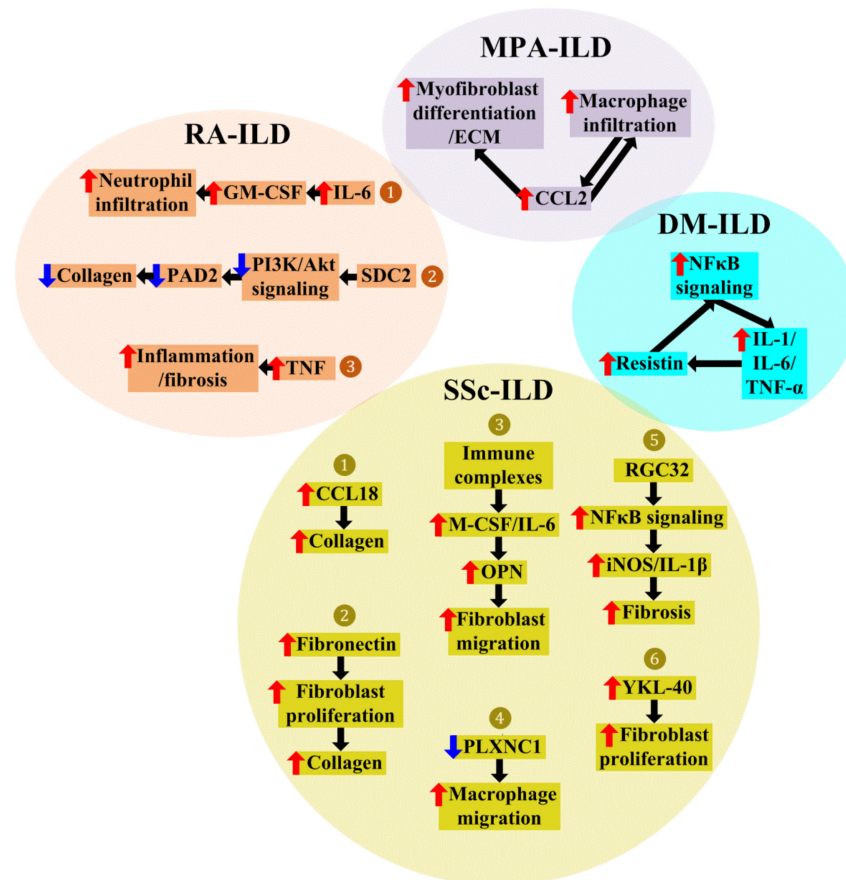
## 4. Roles of Macrophages in CTD-ILD

The evidence mentioned above suggests that macrophages actively participate in the pathogenesis of ILD/PF. In theory, macrophages could also analogously take part in the course of CTD-ILD. This is supported by several observations.

### 4.1. Macrophages in Dermatomyositis (DM)-Associated ILD (DM-ILD)

Although there are no animal models that directly address the molecular mechanisms through which macrophages contribute to DM-ILD, several studies provide indirect evidence implicating macrophages as the main player in DM-ILD. Pathological analyses

show that the infiltration of CD163-positive macrophages into the alveolar spaces is more severe in fatal DM-ILD than in DM-ILD survivors [83], and increased serum CD163 levels are associated with a higher mortality rate in DM-ILD [84]. Similarly, CD206-positive macrophages accumulate more densely in fatal cases of DM-ILD than in DM-ILD survivors, and elevated serum CD206 levels are associated with a higher mortality rate in DM-ILD [84]. Additionally, macrophages express resistin, which is significantly higher in DM-ILD than in DM patients without ILD. Compared with chronic ILD, resistin levels are significantly elevated in rapidly progressive ILD. Acting via nuclear factor kappa B (NFκB) signaling, resistin upregulates IL-1, IL-6, and TNF-α in human monocytes. These proinflammatory cytokines induce resistin expression in macrophages (Figure 2), triggering a self-sustained loop for lung injury [85]. Together, these studies highlight the contribution of macrophages to DM-ILD.



**Figure 2.** Roles of macrophages in CTD-ILD. The figure depicts mechanisms through which macrophages modulate CTD-ILD. In DM-ILD, macrophages express resistin. Resistin activates the NFκB signaling pathway, increasing the secretion of IL-1, IL-6, and TNF-α. This triggers the expression of resistin in macrophages, creating a self-perpetuating reaction to mediate the inflammatory pathogenesis of DM-ILD. In MPA-ILD, macrophages secrete CCL2, which attracts more macrophages to infiltrate. The recruited macrophages produce CCL2, initiating a self-propagating response. Meanwhile, CCL2 stimulates fibroblast differentiation into myofibroblasts and generates ECM, leading to exaggerated lung fibrosis. In RA-ILD, macrophages are implicated in three ways: (1) Exaggerated IL-6 secretion by macrophages triggers the proliferation of GM-CSF-producing T cells, and GM-CSF recruits neutrophil infiltration into the lung, leading to RA-ILD progression. (2) Macrophage-derived SDC2 interferes with PI3K/Akt signaling, decreases PAD2 in fibroblasts, and reduces collagen deposition in the lungs. (3) Macrophages produce high levels of TNF, which leads to an inflammatory phase predominated by cellular infiltration into the lungs and a subsequent shift to a fibrotic phase with irreversible collagen deposition. In SSc-ILD, six pathways are activated by macrophages to drive SSc-ILD: (1) Macrophages produce increased CCL18, which facilitates collagen



production. (2) Macrophages release increased fibronectin, which induces fibroblast proliferation and collagen deposition. (3) Immune complexes stimulate the production of M-CSF and IL-6, which further induce OPN from monocytes. In turn, OPN triggers fibroblast migration, driving fibrosis progression. (4) SSc-ILD shows decreased PLXNC1 expression in macrophages, which boosts macrophage migration. (5) RGC32 promotes iNOS/IL-1 $\beta$ -directed inflammation through NF $\kappa$ B signaling and subsequently enhances the fibrotic response. (6) Macrophage-derived YKL-40, which is increased in SSc-ILD, promotes fibroblast proliferation. Red arrow—increase; Blue arrow—decrease; Black arrow—lead to.

#### 4.2. Macrophages in Microscopic Polyangiitis (MPA)-Associated ILD (MPA-ILD)

In MPA-ILD, macrophage polarization is skewed toward M2, which recruits fibroblasts and transforms them into myofibroblasts, culminating in the formation of lung fibrosis [86]. In the process of M2 polarization, the infiltrated macrophages produce CCL2, which recruits more macrophages to infiltrate the alveolar spaces. The recruited macrophages secrete CCL2, promoting a vicious cycle (Figure 2). In addition, in concert with PDGF secreted by vascular endothelial cells, CCL2 promotes myofibroblast differentiation and ECM production (Figure 2), leading to lung fibrosis [87]. Collectively, these findings implicate macrophages in the pathogenesis of MPA-ILD.

#### 4.3. Macrophages in Rheumatoid Arthritis (RA)-Associated ILD (RA-ILD)

In RA-ILD, autoimmune/complement/interferon cascade genes are altered in macrophages, which might contribute to profibrotic inflammatory lung responses [88]. Several molecules produced by macrophages have been highlighted in the literature (Figure 2).

In RA-ILD, macrophages produce higher IL-6, which promotes the expansion of GM-CSF-producing T cells. GM-CSF is a strong inducer of neutrophil infiltration into the lung and contributes to the progression of RA-ILD in an animal model (Figure 2) [89]. SDC2 in macrophages activates CD148 in fibroblasts, inhibits PI3K/Akt signaling, downregulates PAD2 in fibroblasts, and attenuates collagen production by fibroblasts (Figure 2). The overexpression of SDC2 in alveolar macrophages decreases collagen deposition in the lungs and protects mice from RA-ILD [90]. The augmented secretion of TNF by alveolar macrophages from RA-ILD has been noted [91]. TNF induces an inflammatory phase that is predominated by cellular infiltration to the pulmonary tissue, which subsequently transitions to a fibrotic phase that constitutes the “irreversible” process of collagen deposition in the pulmonary parenchyma, resulting in RA-ILD in a murine model (Figure 2) [92].

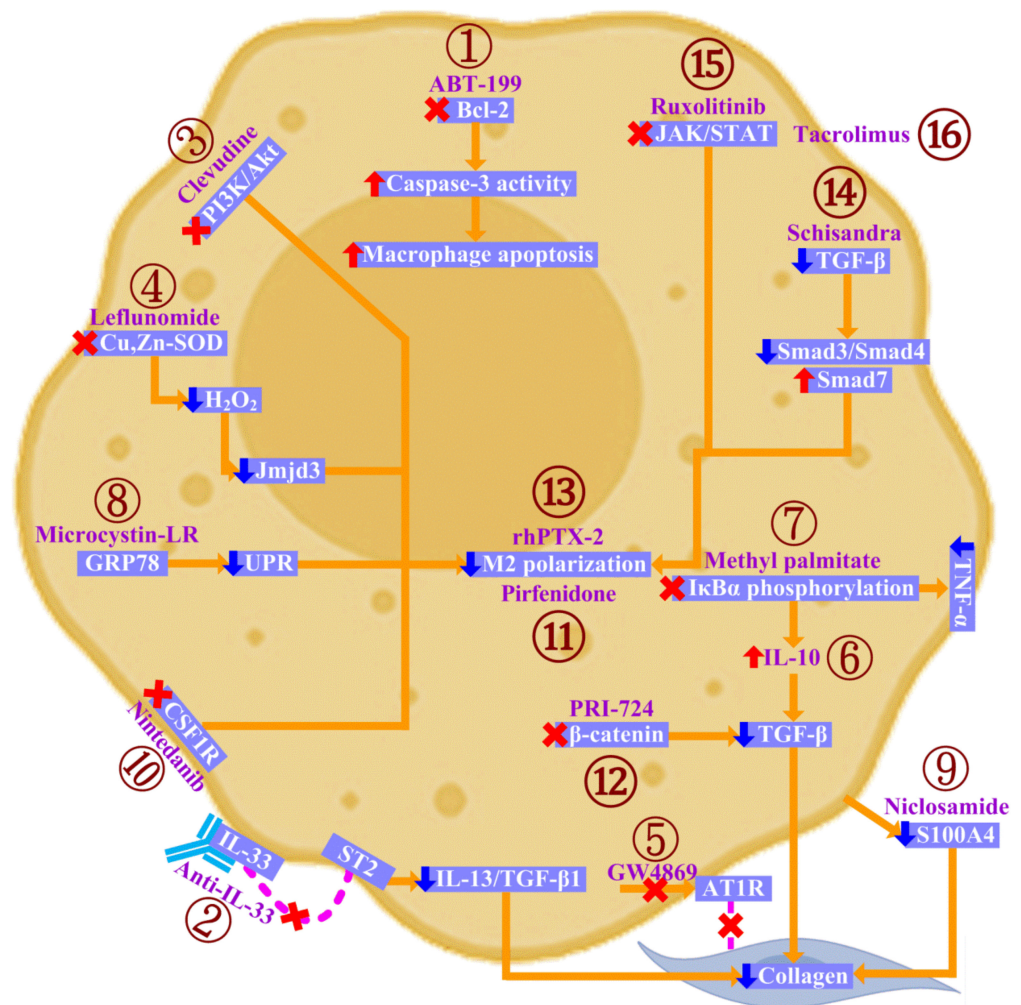
#### 4.4. Macrophages in Systemic Sclerosis (SSc)-Associated ILD (SSc-ILD)

In SSc-ILD, macrophages express profibrotic factors that promote the differentiation, migration, and activation of fibroblasts, suggesting the involvement of macrophages in SSc-ILD [25]. Currently, there are several known mechanisms that macrophages utilize to modulate SSc-ILD (Figure 2). (1) Monocytes from SSc-ILD patients reveal a profibrotic phenotype characterized by the expression of CD163 and the enhanced secretion of CCL18 [93], which promotes collagen production (Figure 2) [40]. (2) At the same time, SSc-ILD macrophages release significantly more fibronectin, which leads to fibroblast proliferation and subsequent collagen deposition (Figure 2) [64,93]. (3) Immunologically, immune complexes (ICs) activate human monocytes to secrete M-CSF and IL-6, which in turn induce osteopontin (OPN) from monocytes. Next, OPN facilitates fibroblast migration to areas adjacent to the fibrotic niche, thereby aiding lung fibrosis progression (Figure 2) [94]. (4) Meanwhile, PLXNC1 expression is reduced in SSc-ILD macrophages, which could lead to the excess migration of macrophages (Figure 2), amplifying fibrosis [46]. (5) Moreover, the response gene to complement 32 (RGC32) is abundantly expressed in macrophages, activates NF $\kappa$ B signaling, and promotes inflammatory gene expression by binding to their promoters. RGC32 deficiency in mice impairs the polarization of classically activated macrophages, attenuates the expression of inflammatory mediators in macrophages, including the fibrosis inducers iNOS and IL-1 $\beta$ , which are regulated by NF $\kappa$ B, and significantly ameliorates lung fibrosis (Figure 2) [95]. (6) YKL-40 is elevated in SSc-ILD. Macrophages produce YKL-40,

which exerts promitogenic effects on lung fibroblasts (Figure 2) [96]. These findings all support the central roles of macrophages in SSc-ILD.

### 5. Targeting Macrophages in CTD-ILD

It is hoped that, apart from detailing our current understanding of CTD-ILD pathogenesis, this knowledge could be leveraged to create therapeutic strategies to combat CTD-ILD. However, similar to the understanding of disease pathogenesis, most therapeutic strategies that target macrophages in CTD-ILD originated from studies targeting macrophages in PF. Therefore, in the following section, we review therapeutic strategies to target macrophages in preclinical or clinical models of PF or CTD-ILD (Figure 3):



**Figure 3.** Potential agents to target macrophages in CTD-ILD. The figure depicts potential strategies to target macrophages in the context of CTD-ILD according to the literature. (1) ABT-199 inhibits Bcl-2. As a result, ABT-199 augments caspase-3 activity and enhances macrophage apoptosis, counteracting lung fibrosis. (2) Anti-IL-33 blocks IL-33 action on ST2 and thereby downregulates IL-13 and TGF-β1 production, which decreases collagen synthesis by fibroblasts. (3) Clevudine, as an inhibitor of the PI3K/Akt signaling pathway, prevents M2 polarization and the subsequent fibrotic response of the lungs. (4) By inhibiting Cu,Zn-SOD-mediated H<sub>2</sub>O<sub>2</sub> generation, leflunomide downregulates Jmjd3 expression, lowers M2 polarization, and diminishes lung fibrosis. (5) GW4869, which eliminates the secretion of AT1R-carrying exosomes from macrophages, decreases collagen synthesis in fibroblasts and ameliorates lung fibrosis. (6) IL-10 curbs TGF-β production in macrophages and prevents collagen deposition by fibroblasts. (7) Methyl palmitate blocks IκBα phosphorylation, reducing TNF-α and boosting IL-10 expression in macrophages, which inhibit lung inflammation and fibrosis. (8) After binding to GRP78, microcystin-LR interferes with UPR signaling, subsequently preventing M2 macrophage polarization

and leading to attenuated lung fibrosis. (9) Niclosamide interferes with S100A4 production by macrophages, which ameliorates collagen production by fibroblasts. These changes culminate in reducing the fibrosis of the lungs. (10) Nintedanib limits M2 differentiation by blocking CSF1R and consequently improves fibrosis in a CTD-ILD model. (11) Pirfenidone acts on macrophages to block M2 polarization and, as a result, suppresses fibroblast proliferation and restricts lung fibrosis. (12) The  $\beta$ -catenin pathway inhibitor PRI-724, which blocks  $\beta$ -catenin signaling, lowers TGF- $\beta$  production in macrophages and contributes to mitigated collagen production by fibroblasts. (13) rhPTX-2 prevents M2 differentiation and avoids PF deterioration. (14) Schisandra reduces TGF- $\beta$  and downstream Smad3/Smad4 while stimulating Smad7 production. These signaling events disrupt M2 polarization and thereby improving lung fibrosis. (15) Ruxolitinib and (16) Tacrolimus, by inhibiting JAK/STAT signaling, suppress M2 polarizations and hence improve lung fibrosis in an animal model. Red arrow—increase; blue arrow—decrease; cross symbol—block; dashed line—act on.

(1) ABT-199: ABT-199, an inhibitor of Bcl-2, is a potential therapeutic agent that prevents fibrosis progression. Bcl-2 decreases caspase-3 activity, mediating the apoptosis resistance of macrophages, which facilitates lung fibrosis (Figure 3). Mice have lung fibrosis resolution when treated with ABT-199 after fibrosis is established [36].

(2) Anti-IL-33: IL-33 is induced in macrophages during PF. Acting through ST2, IL-33 polarizes M2 macrophages to increase IL-13 and TGF- $\beta$ 1 production. This activates fibroblasts and stimulates fibroblast proliferation. Therefore, IL-33 enhances collagen synthesis by fibroblasts and amplifies the fibrosis of the lung. Accordingly, an anti-IL-33 antibody reduces lung fibrosis (Figure 3) [97].

(3) Clevudine: Clevudine is a purine nucleoside analog indicated for hepatitis B virus (HBV) treatment. Interestingly, clevudine can inhibit the PI3K/Akt signaling and therefore suppresses M2 differentiation. Correspondingly, epithelial-to-mesenchymal transition (EMT) and M2-induced myofibroblast activation are alleviated (Figure 3), thus preventing profibrotic cytokine secretion and downstream collagen deposition, with a concomitant attenuation of fibrotic processes in the lungs [98].

(4) Leflunomide: Leflunomide inhibits Cu,Zn-SOD-mediated H<sub>2</sub>O<sub>2</sub> generation. Consequently, Jmjd3 expression is reduced, preventing macrophage M2 polarization and thereby attenuating lung tissue fibrosis (Figure 3) [49].

(5) GW4869: Macrophages secrete exosomes carrying AT1R, which are taken up by fibroblasts, activating collagen synthesis. GW4869, by inhibiting exosome secretion, attenuates fibrosis in a mouse model (Figure 3) [62].

(6) IL-10: IL-10 suppresses TGF- $\beta$  production in macrophages and subsequently decreases collagen production in fibroblasts (Figure 3), diminishing the intensity of pulmonary tissue fibrosis [99].

(7) Methyl palmitate: Methyl palmitate inhibits the phosphorylation of inhibitory kappa B alpha (I $\kappa$ B $\alpha$ ), resulting in decreased TNF- $\alpha$  and increased IL-10 production by macrophages (Figure 3). These changes ameliorate lung inflammation and fibrosis [100].

(8) Microcystin-leucine arginine (LR): The binding of microcystin-LR to glucose-regulated protein 78 kDa (GRP78) suppresses endoplasmic reticulum unfolded protein response (UPR) signaling, which inhibits M2 macrophage polarization (Figure 3) and leads to attenuated EMT and fibroblast–myofibroblast transition (FMT). As a result, microcystin-LR exerts a therapeutic effect on lung fibrosis [101].

(9) Niclosamide: S100A4 is secreted by M2 macrophages to enhance collagen production in lung fibroblasts. The inhibition of S100A4 production with niclosamide reduces collagen deposition and attenuates lung fibrosis (Figure 3) [75].

(10) Nintedanib: By inhibiting CSF1R, nintedanib blocks the M2 differentiation of monocytes (Figure 3), which reduces macrophage activation and ameliorates fibrosis in a CTD-ILD model [102].

(11) Pirfenidone: Pirfenidone has an indirect inhibitory effect on fibroblast proliferation by suppressing macrophage polarization toward the M2 phenotype (Figure 3), which is therefore helpful for lung fibrosis [103].



(12) PRI-724:  $\beta$ -catenin signaling promotes the TGF- $\beta$  expression of macrophages, which contributes to collagen synthesis in fibroblasts. As a result, the  $\beta$ -catenin pathway inhibitor PRI-724 inhibits the production of TGF- $\beta$  by alveolar macrophages and ameliorates collagen deposition in fibrotic lungs (Figure 3) [79,104].

(13) Recombinant human pentraxin-2 (rhPTX-2): Pentraxin-2, also called serum amyloid P (SAP), reduces M2 differentiation and subsequent lung fibrosis (Figure 3) [80,81]. In line with this, rhPTX-2 prevents the deterioration of lung function in PF patients [105].

(14) Schisandra: Schisandra decreases TGF- $\beta$ , reduces the levels of Smad3 and Smad4, and upregulates Smad7, suppressing M2 macrophage polarization (Figure 3). Accordingly, Schisandra exerts protective effects on lung fibrosis [106].

(15) Ruxolitinib: In CTD-ILD, ruxolitinib, which inhibits JAK/STAT, prevents the upregulation of proinflammatory molecules (CXCL10, IFI44, NOS2, and TNF- $\alpha$ ) and profibrotic molecules (ARG1, CHI3L3, FLT1, IL4Ra, and RETNLA) (Figure 3). Ruxolitinib concomitantly reduces M2 polarization and the mononuclear pulmonary infiltrate, leading to significantly reduced CTD-ILD in an animal model [107].

(16) Tacrolimus: In the animal model of PF, tacrolimus inhibits signaling of JAK/STAT pathways and suppresses M2 polarization and M2-induced myofibroblast activation, thereby alleviating PF progression [108].

## 6. Investigational Agents in Preclinical and Clinical Trials of CTD-ILD

In practice, there is no standard treatment protocol for CTD-ILD. However, considering the autoimmune nature of CTDs, immunomodulatory drugs are the cornerstones in the pharmacologic treatment of CTD-ILD [109]. Considering these uncertainties, therapies that address the ILD component of CTD are currently a field of active research [110]. According to [clinicaltrials.gov](https://clinicaltrials.gov) (accessed on 25 March 2023), 39 clinical trials exploring the therapeutic effects of various agents for CTD-ILD have been planned or are already underway or completed (Table 3). Of the 16 therapeutic agents that act on non-macrophage cells, three (Cyclophosphamide, Mycophenolate Mofetil, and Tadalafil) exhibit therapeutic effects. Of the four therapeutic agents which act on macrophages, three (Nintedanib, Pirfenidone, and Tacrolimus) exhibit therapeutic effects, which is borderline higher than the percentage of agents which act on non-macrophage cells ( $p = 0.06$  by Fisher's Exact Test). However, most available clinical trials examined agents which act on non-macrophage cells (25 clinical trials) rather than agents that act on macrophage cells (14 clinical trials). Therefore, it is hoped that future clinical trials will focus more on macrophage-directed agents.

**Table 3.** Efficacy of investigational agents in clinical trials of CTD-ILD in [clinicaltrials.gov](https://clinicaltrials.gov).

| Agents                | Targeted Cells         | Diseases                               | Study       | Outcome <sup>a</sup>                    |
|-----------------------|------------------------|--|-------------|---|
| Abatacept             | T cells [111]          | Antisynthetase syndrome-associated ILD | NCT03215927 | Active                                  |
| Abatacept             | T cells [111]          | RA-ILD                                 | NCT03084419 | Unknown                                 |
| Abituzumab            | Epithelial cells [112] | SSc-ILD                                | NCT02745145 | Terminated due to slow enrollment [112] |
| Basiliximab           | Lymphocytes [113]      | DM-ILD                                 | NCT03192657 | Unknown                                 |
| Belimumab             | B cells [114]          | SSc-ILD                                | NCT05878717 | Not yet recruiting                      |
| Bortezomib            | Fibroblasts [115]      | SSc-ILD                                | NCT02370693 | Completed                               |
| Bosentan              | Fibroblasts [116]      | SSc-ILD                                | NCT00070590 | Ineffective [117]                       |
| Bosentan              | Fibroblasts [116]      | SSc-ILD                                | NCT00319033 | Completed                               |
| Cyclophosphamide      | Lymphocytes [118]      | Antisynthetase syndrome-associated ILD | NCT03770663 | Recruiting                              |
| Cyclophosphamide      | Lymphocytes [118]      | SSc-ILD                                | NCT00883129 | Improve [119]                           |
| Cyclophosphamide      | Lymphocytes [118]      | SSc-ILD                                | NCT01570764 | Completed                               |
| Cyclosporin A         | T cells [120]          | Sjogren's syndrome-associated ILD      | NCT02370550 | Unknown                                 |
| Ixazomib              | Fibroblasts [121]      | SSc-ILD                                | NCT04837131 | Recruiting                              |
| Mycophenolate mofetil | Lymphocytes [122]      | Myositis-associated ILD                | NCT05129410 | Recruiting                              |



Table 3. Cont.

| Agents                | Targeted Cells                         | Diseases                | Study       | Outcome <sup>a</sup>                                   |
|-----------------------|--|-------------------------|-------------|--|
| Mycophenolate mofetil | Lymphocytes [122]                      | SSc-ILD                 | NCT00883129 | Improve [119]  |
| Mycophenolate mofetil | Lymphocytes [122]                      | SSc-ILD                 | NCT02896205 | Ineffective [123]                                      |
| Mycophenolate mofetil | Lymphocytes [122]                      | SSc-ILD                 | NCT05785065 | Not yet recruiting                                     |
| N-acetylcysteine      | Macrophages [124]                      | CTD-ILD                 | NCT01424033 | Terminated due to departure of principal investigator. |
| Nintedanib            | Macrophages                            | Myositis-associated ILD | NCT05335278 | Recruiting   |
| Nintedanib            | Macrophages                            | Myositis-associated ILD | NCT05799755 | Not yet recruiting                                     |
| Nintedanib            | Macrophages                            | SSc-ILD                 | NCT02597933 | Effective [125]  |
| Nintedanib            | Macrophages                            | SSc-ILD                 | NCT03313180 | Completed  |
| Pirfenidone           | Macrophages                            | CTD-ILD                 | NCT04928586 | Recruiting   |
| Pirfenidone           | Macrophages                            | CTD-ILD                 | NCT05505409 | Recruiting   |
| Pirfenidone           | Macrophages                            | DM-ILD                  | NCT02821689 | Unknown  |
| Pirfenidone           | Macrophages                            | DM-ILD                  | NCT03857854 | Unknown  |
| Pirfenidone           | Macrophages                            | RA-ILD                  | NCT02808871 | Slow FVC decline [126]                                 |
| Pirfenidone           | Macrophages                            | SSc-ILD                 | NCT03221257 | Completed  |
| Pirfenidone           | Macrophages                            | SSc-ILD                 | NCT03856853 | Unknown  |
| Pomalidomide          | T cells [127]                          | SSc-ILD                 | NCT01559129 | Discontinued [127]                                     |
| PRA023                | Fibroblasts [128]                      | SSc-ILD                 | NCT05270668 | Recruiting   |
| Rituximab             | B cells [129]                          | CTD-ILD                 | NCT01862926 | Not superior to cyclophosphamide [129]                 |
| Rituximab             | B cells [129]                          | RA-ILD                  | NCT00578565 | Inconclusive   |
| Tacrolimus            | Macrophages                            | Myositis-associated ILD | NCT00504348 | Improve [130]  |
| Tacrolimus            | Macrophages                            | Myositis-associated ILD | NCT02159651 | Improve [131]  |
| Tadalafil             | Fibroblasts [132]                      | SSc-ILD                 | NCT01553981 | Improve [133]  |
| Tofacitinib           | Myeloid derived suppressor cells [134] | RA-ILD                  | NCT04311567 | Recruiting   |
| Tofacitinib           | Myeloid derived suppressor cells [134] | RA-ILD                  | NCT05246293 | Recruiting   |
| Vixarelimab           | Fibroblasts [135,136]                  | SSc-ILD                 | NCT05785624 | Recruiting   |

<sup>a</sup> Recorded at [clinicaltrials.gov](https://clinicaltrials.gov) or in the literature. FVC: functional vital capacity. Unknown: no result has been posted, or the recruitment status is unknown.

## 7. Concluding Remarks and Future Directions

Despite the significant morbidities and mortalities caused by CTD-ILD, publications detailing how macrophages contribute to ILD in the context of CTD are scarce. More research is necessary to elucidate the distinct roles of specific lung macrophage populations in the CTD-ILD, with the aim of providing new insights into the development of macrophage-directed therapeutic targets and diagnostic tools [31]. Current knowledge is mostly extrapolated from findings on animal models of PF. However, well-established mouse macrophage counterparts might not always be available in humans. A humanized mouse model in which mice are transplanted with alveolar organoids and hematopoietic stem and progenitor cells could be exploited to overcome these issues [69]. Blocking macrophage molecular mechanisms, boosting macrophage signaling pathways, or combinations of these may prove fruitful and provide opportunities to relieve the paucity of proven effective treatments [137] and meet the clinical needs of CTD-ILD. The literature shows that aiming at specific cell types is a viable choice for several disease entities [138–140], especially CTDs [141,142]. Several systemic reviews also suggest the therapeutic potential of targeting specific cells in CTD-ILD [143,144]. Moreover, the pathogenesis of CTD-ILD involves other cell types (such as lymphocytes and fibroblasts) whose crosstalk with macrophages requires further characterization [74]. Deciphering these interactions could be another direction of research. We hope that our efforts to elucidate the pathophysiology of ILD macrophages in the context of CTD will offer new insights into the development of macrophage-directed therapeutic approaches for this group of debilitating diseases.

**Author Contributions:** Conceptualization, C.-C.T., W.-T.L. and J.-H.Y.; investigation, K.-Y.C., P.-Y.W. and C.-Y.Y.; data curation, Y.-W.S., W.-Y.S., C.-C.W., T.-T.O., W.-C.T., C.-J.C., S.-C.L. and S.-J.C.; writing—original draft preparation, C.-C.T. and K.-Y.C.; writing—review and editing, C.-C.T., W.-T.L. and J.-H.Y.; supervision, W.-T.L. and J.-H.Y. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Spagnolo, P.; Distler, O.; Ryerson, C.J.; Tzouveleakis, A.; Lee, J.S.; Bonella, F.; Bouros, D.; Hoffmann-Vold, A.M.; Crestani, B.; Matteson, E.L. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). *Ann. Rheum. Dis.* **2021**, *80*, 143–150. [[CrossRef](#)] [[PubMed](#)]
2. Silva, M.; Fernandes, A.; Pereira, A.R.; Madanelo, S.; Clemêncio, T.; Ferreira, P.G. Awareness towards the main ILD among primary care physicians. *Multidiscip. Respir. Med.* **2022**, *17*, 848. [[CrossRef](#)] [[PubMed](#)]
3. Fisseler-Eckhoff, A.; Märker-Hermann, E. Interstitial lung disease associated with connective tissue disease. *Pathologe* **2021**, *42*, 4–10. [[CrossRef](#)] [[PubMed](#)]
4. Yoo, H.; Hino, T.; Han, J.; Franks, T.J.; Im, Y.; Hatabu, H.; Chung, M.P.; Lee, K.S. Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality (ILA): Evolving concept of CT findings, pathology and management. *Eur. J. Radiol. Open* **2021**, *8*, 100311. [[CrossRef](#)]
5. Ahmed, S.; Handa, R. Management of Connective Tissue Disease-related Interstitial Lung Disease. *Curr. Pulmonol. Rep.* **2022**, *11*, 86–98. [[CrossRef](#)]
6. Mena-Vázquez, N.; Godoy-Navarrete, F.J.; Lisbona-Montañez, J.M.; Redondo-Rodríguez, R.; Manrique-Arija, S.; Rioja, J.; Mucientes, A.; Ruiz-Limón, P.; Garcia-Studer, A.; Ortiz-Márquez, F.; et al. Inflammatory Biomarkers in the Diagnosis and Prognosis of Rheumatoid Arthritis-Associated Interstitial Lung Disease. *Int. J. Mol. Sci.* **2023**, *24*, 6800. [[CrossRef](#)]
7. Dsouza, K.G.; Alexander, A.S.; Watts, J.R.; Kulkarni, T. Management of interstitial lung disease in patients with autoimmune disease-related interstitial lung disease. *Multidiscip. Respir. Med.* **2023**, *18*, 890. [[CrossRef](#)]
8. Ng, K.H.; Chen, D.Y.; Lin, C.H.; Chao, W.C.; Chen, Y.M.; Chen, Y.H.; Huang, W.N.; Hsieh, T.Y.; Lai, K.L.; Tang, K.T.; et al. Risk of interstitial lung disease in patients with newly diagnosed systemic autoimmune rheumatic disease: A nationwide, population-based cohort study. *Semin. Arthritis Rheum.* **2020**, *50*, 840–845. [[CrossRef](#)]
9. Chen, F.; Wang, J.; Zhang, P.; Zuo, Y.; Ye, L.; Wang, G.; Shu, X. Interstitial Lung Disease in Dermatomyositis Without Myositis-Specific and Myositis-Associated Autoantibodies: Study of a Series of 72 Patients from a Single Cohort. *Front. Immunol.* **2022**, *13*, 879266. [[CrossRef](#)]
10. Lu, J.; Liu, C.; Zhou, X.; Tang, J.; Liu, S.; Tang, M.; Li, M.; Zhu, L. Palmar erythema and palmar papules as predictors for dermatomyositis-related acute/subacute interstitial lung disease: A retrospective study. *Rheumatology* **2021**, *61*, 413–421. [[CrossRef](#)]
11. Weng, C.; Ding, Z.; Zhou, Y.; Yang, Q.; Xue, L.; Zhang, L.; Wang, G.; Liu, Z. Clinical Characteristics of Dermatomyositis with Interstitial Lung Disease: A Retrospective Case-Control Study. *Rheumatol. Ther.* **2023**, *10*, 635–648. [[CrossRef](#)]
12. Wang, Q.; Gao, C.; Zhang, C.; Yao, M.; Liang, W.; Sun, W.; Zheng, Z. Tumor markers are associated with rapidly progressive interstitial lung disease in adult-dermatomyositis. *Clin. Rheumatol.* **2022**, *41*, 1731–1739. [[CrossRef](#)]
13. Pérez, N.; Gargiulo, M.L.Á.; Suarez, L.; Khoury, M.; Gómez, G. Clinical characteristics and prognostic factors in an Argentinian cohort with ANCA-associated vasculitis. *Medicina* **2021**, *81*, 198–207.
14. Sweis, J.J.G.; Sweis, N.W.G.; Alnaimat, F.; Jansz, J.; Liao, T.E.; Alsakaty, A.; Azam, A.; Elmergawy, H.; Hanson, H.A.; Ascoli, C.; et al. Immune-mediated lung diseases: A narrative review. *Front. Med.* **2023**, *10*, 1160755. [[CrossRef](#)]
15. Matsuda, S.; Kotani, T.; Suzuka, T.; Kiboshi, T.; Fukui, K.; Wakama, M.; Ishida, T.; Fujiki, Y.; Shiba, H.; Nagai, K.; et al. Evaluation of poor prognostic factors of respiratory related death in microscopic polyangiitis complicated by interstitial lung disease. *Sci. Rep.* **2021**, *11*, 1490. [[CrossRef](#)]
16. Takakuwa, Y.; Yamasaki, Y.; Matsushita, H.; Kiyokawa, T.; Mizushima, M.; Tonooka, K.; Nagafuchi, H.; Matsuoka, S.; Ooka, S.; Kawahata, K. Long-term survival, causes of death, and prognostic factors for mortality in patients with microscopic polyangiitis and those with anti-neutrophil cytoplasmic antibody-positive interstitial lung disease: A single-center retrospective study. *Int. J. Rheum. Dis.* **2023**, *26*, 446–453. [[CrossRef](#)]
17. Fidler, L.; Widdifield, J.; Fisher, J.H.; Shapera, S.; Gershon, A.S. Rheumatoid arthritis associated interstitial lung disease: Trends in epidemiology and mortality in Ontario from 2000 to 2018. *Respir. Med.* **2023**, *in press*. [[CrossRef](#)]

18. Ng, K.H.; Chen, D.Y.; Lin, C.H.; Chao, W.C.; Chen, H.H. Analysis of risk factors of mortality in rheumatoid arthritis patients with interstitial lung disease: A nationwide, population-based cohort study in Taiwan. *RMD Open* **2022**, *8*, e002343. [[CrossRef](#)]
19. Sparks, J.A.; Jin, Y.; Cho, S.K.; Vine, S.; Desai, R.; Doyle, T.J.; Kim, S.C. Prevalence, incidence and cause-specific mortality of rheumatoid arthritis-associated interstitial lung disease among older rheumatoid arthritis patients. *Rheumatology* **2021**, *60*, 3689–3698. [[CrossRef](#)]
20. Reid, P.; Guler, S.A. Mortality Trends in Rheumatoid Arthritis: Zooming in on Interstitial Lung Disease. *Ann. Am. Thorac. Soc.* **2021**, *18*, 1953–1954. [[CrossRef](#)]
21. Panagopoulos, P.; Goules, A.; Hoffmann-Vold, A.M.; Matteson, E.L.; Tzioufas, A. Natural history and screening of interstitial lung disease in systemic autoimmune rheumatic disorders. *Ther. Adv. Musculoskelet. Dis.* **2021**, *13*, 1759720X211037519. [[CrossRef](#)] [[PubMed](#)]
22. Li, Q.; Wallace, L.; Patnaik, P.; Alves, M.; Gahlemann, M.; Kohlbrenner, V.; Raabe, C.; Wang, J.R.; Garry, E.M. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: A US cohort study. *Rheumatology* **2021**, *60*, 1915–1925. [[CrossRef](#)] [[PubMed](#)]
23. Hoffmann-Vold, A.M.; Fretheim, H.; Halse, A.K.; Seip, M.; Bitter, H.; Wallenius, M.; Garen, T.; Salberg, A.; Brunborg, C.; Midtvedt, Ø.; et al. Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, 1258–1266. [[CrossRef](#)]
24. Hyldgaard, C.; Bendstrup, E.; Pedersen, A.B.; Pedersen, L.; Ellingsen, T. Interstitial Lung Disease in Connective Tissue Diseases: Survival Patterns in a Population-Based Cohort. *J. Clin. Med.* **2021**, *10*, 4830. [[CrossRef](#)] [[PubMed](#)]
25. Chen, S.; Saeed, A.F.U.H.; Liu, Q.; Jiang, Q.; Xu, H.; Xiao, G.G.; Rao, L.; Duo, Y. Macrophages in immunoregulation and therapeutics. *Signal Transduct. Target. Ther.* **2023**, *8*, 207. [[CrossRef](#)]
26. Moreira, A.C.; Silva, T.; Mesquita, G.; Gomes, A.C.; Bento, C.M.; Neves, J.V.; Rodrigues, D.F.; Rodrigues, P.N.; Almeida, A.A.; Santambrogio, P.; et al. H-Ferritin Produced by Myeloid Cells Is Released to the Circulation and Plays a Major Role in Liver Iron Distribution during Infection. *Int. J. Mol. Sci.* **2021**, *23*, 269. [[CrossRef](#)]
27. Enomoto, N. Pathological Roles of Pulmonary Cells in Acute Lung Injury: Lessons from Clinical Practice. *Int. J. Mol. Sci.* **2022**, *23*, 15027. [[CrossRef](#)]
28. Hofbauer, D.; Mougiakakos, D.; Brogini, L.; Zaiss, M.; Büttner-Herold, M.; Bach, C.; Spriewald, B.; Neumann, F.; Bisht, S.; Nolting, J.; et al.  $\beta_2$ -microglobulin triggers NLRP3 inflammasome activation in tumor-associated macrophages to promote multiple myeloma progression. *Immunity* **2021**, *54*, 1772–1787.e9. [[CrossRef](#)]
29. Chen, J.; Zhang, R.; Xie, M.; Luan, C.; Li, X. Transcriptome Sequencing Identifies PLAUR as an Important Player in Patients with Dermatomyositis-Associated Interstitial Lung Disease. *Front. Genet.* **2021**, *12*, 784215. [[CrossRef](#)]
30. Yang, Y.; Yin, G.; Hao, J.; Xie, Q.; Liu, Y. Serum Interleukin-18 Level is Associated with Disease Activity and Interstitial Lung Disease in Patients with Dermatomyositis. *Arch. Rheumatol.* **2017**, *32*, 181–188. [[CrossRef](#)]
31. Byrne, A.J.; Maher, T.M.; Lloyd, C.M. Pulmonary Macrophages: A New Therapeutic Pathway in Fibrosing Lung Disease? *Trends Mol. Med.* **2016**, *22*, 303–316. [[CrossRef](#)] [[PubMed](#)]
32. Koo, B.S.; Park, K.Y.; Lee, H.J.; Kim, H.J.; Ahn, H.S.; Yim, S.Y.; Jun, J.B. Effect of combined pulmonary fibrosis and emphysema on patients with connective tissue diseases and systemic sclerosis: A systematic review and meta-analysis. *Arthritis Res. Ther.* **2021**, *23*, 100. [[CrossRef](#)] [[PubMed](#)]
33. Misharin, A.V.; Morales-Nebreda, L.; Reyfman, P.A.; Cuda, C.M.; Walter, J.M.; McQuattie-Pimentel, A.C.; Chen, C.I.; Anekalla, K.R.; Joshi, N.; Williams, K.J.N.; et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. *J. Exp. Med.* **2017**, *214*, 2387–2404. [[CrossRef](#)]
34. Aegerter, H.; Lambrecht, B.N.; Jakubzick, C.V. Biology of lung macrophages in health and disease. *Immunity* **2022**, *55*, 1564–1580. [[CrossRef](#)] [[PubMed](#)]
35. Aran, D.; Looney, A.P.; Liu, L.; Wu, E.; Fong, V.; Hsu, A.; Chak, S.; Naikawadi, R.P.; Wolters, P.J.; Abate, A.R.; et al. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. *Nat. Immunol.* **2019**, *20*, 163–172. [[CrossRef](#)] [[PubMed](#)]
36. Gu, L.; Surolia, R.; Larson-Casey, J.L.; He, C.; Davis, D.; Kang, J.; Antony, V.B.; Carter, A.B. Targeting Cpt1a-Bcl-2 interaction modulates apoptosis resistance and fibrotic remodeling. *Cell Death Differ.* **2022**, *29*, 118–132. [[CrossRef](#)]
37. Ishida, Y.; Kuninaka, Y.; Mukaida, N.; Kondo, T. Immune Mechanisms of Pulmonary Fibrosis with Bleomycin. *Int. J. Mol. Sci.* **2023**, *24*, 3149. [[CrossRef](#)]
38. Liu, S.; Liu, C.; Wang, Q.; Min, J. CC Chemokines in Idiopathic Pulmonary Fibrosis: Pathogenic Role and Therapeutic Potential. *Biomolecules* **2023**, *13*, 333. [[CrossRef](#)]
39. Stahl, M.; Schupp, J.; Jäger, B.; Schmid, M.; Zissel, G.; Müller-Quernheim, J.; Prasse, A. Lung collagens perpetuate pulmonary fibrosis via CD204 and M2 macrophage activation. *PLoS ONE* **2013**, *8*, e81382. [[CrossRef](#)]
40. Zhang, L.; Wang, Y.; Wu, G.; Xiong, W.; Gu, W.; Wang, C.Y. Macrophages: Friend or foe in idiopathic pulmonary fibrosis? *Respir. Res.* **2018**, *19*, 170.
41. Li, J.; Zhai, X.; Sun, X.; Cao, S.; Yuan, Q.; Wang, J. Metabolic reprogramming of pulmonary fibrosis. *Front. Pharmacol.* **2022**, *13*, 1031890. [[CrossRef](#)]

42. Xie, N.; Cui, H.; Ge, J.; Banerjee, S.; Guo, S.; Dubey, S.; Abraham, E.; Liu, R.M.; Liu, G. Metabolic characterization and RNA profiling reveal glycolytic dependence of profibrotic phenotype of alveolar macrophages in lung fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2017**, *313*, L834–L844. [[CrossRef](#)]
43. Liu, S.; Lv, X.; Wei, X.; Liu, C.; Li, Q.; Min, J.; Hua, F.; Zhang, X.; Li, K.; Li, P.; et al. TRIB3–GSK-3 $\beta$  interaction promotes lung fibrosis and serves as a potential therapeutic target. *Acta Pharm. Sin. B* **2021**, *11*, 3105–3119. [[CrossRef](#)]
44. Philip, K.; Mills, T.W.; Davies, J.; Chen, N.Y.; Karmouty-Quintana, H.; Luo, F.; Molina, J.G.; Amione-Guerra, J.; Sinha, N.; Guha, A.; et al. HIF1A up-regulates the ADORA2B receptor on alternatively activated macrophages and contributes to pulmonary fibrosis. *FASEB J.* **2017**, *31*, 4745–4758. [[CrossRef](#)]
45. Ogger, P.P.; Albers, G.J.; Hewitt, R.J.; O’Sullivan, B.J.; Powell, J.E.; Calamita, E.; Ghai, P.; Walker, S.A.; McErlean, P.; Saunders, P.; et al. Itaconate controls the severity of pulmonary fibrosis. *Sci. Immunol.* **2020**, *5*, eabc1884. [[CrossRef](#)]
46. Peng, X.; Moore, M.; Mathur, A.; Zhou, Y.; Sun, H.; Gan, Y.; Herazo-Maya, J.D.; Kaminski, N.; Hu, X.; Pan, H.; et al. Plexin C1 deficiency permits synaptotagmin 7-mediated macrophage migration and enhances mammalian lung fibrosis. *FASEB J.* **2016**, *30*, 4056–4070. [[CrossRef](#)] [[PubMed](#)]
47. Goda, C.; Balli, D.; Black, M.; Milewski, D.; Le, T.; Ustiyani, V.; Ren, X.; Kalinichenko, V.V.; Kalin, T.V. Loss of FOXM1 in macrophages promotes pulmonary fibrosis by activating p38 MAPK signaling pathway. *PLoS Genet.* **2020**, *16*, e1008692. [[CrossRef](#)] [[PubMed](#)]
48. He, C.; Ryan, A.J.; Murthy, S.; Carter, A.B. Accelerated development of pulmonary fibrosis via Cu,Zn-superoxide dismutase-induced alternative activation of macrophages. *J. Biol. Chem.* **2013**, *288*, 20745–20757. [[CrossRef](#)] [[PubMed](#)]
49. He, C.; Larson-Casey, J.L.; Gu, L.; Ryan, A.J.; Murthy, S.; Carter, A.B. Cu,Zn-Superoxide Dismutase-Mediated Redox Regulation of Jumonji Domain Containing 3 Modulates Macrophage Polarization and Pulmonary Fibrosis. *Am. J. Respir. Cell Mol. Biol.* **2016**, *55*, 58–71. [[CrossRef](#)]
50. Guo, X.; Li, T.; Xu, Y.; Xu, X.; Zhu, Z.; Zhang, Y.; Xu, J.; Xu, K.; Cheng, H.; Zhang, X.; et al. Increased levels of Gab1 and Gab2 adaptor proteins skew interleukin-4 (IL-4) signaling toward M2 macrophage-driven pulmonary fibrosis in mice. *J. Biol. Chem.* **2017**, *292*, 14003–14015. [[CrossRef](#)]
51. Pan, T.; Zhou, Q.; Miao, K.; Zhang, L.; Wu, G.; Yu, J.; Xu, Y.; Xiong, W.; Li, Y.; Wang, Y. Suppressing Sart1 to modulate macrophage polarization by siRNA-loaded liposomes: A promising therapeutic strategy for pulmonary fibrosis. *Theranostics* **2021**, *11*, 1192–1206. [[CrossRef](#)] [[PubMed](#)]
52. Zhao, J.; Okamoto, Y.; Asano, Y.; Ishimaru, K.; Aki, S.; Yoshioka, K.; Takuwa, N.; Wada, T.; Inagaki, Y.; Takahashi, C.; et al. Sphingosine-1-phosphate receptor-2 facilitates pulmonary fibrosis through potentiating IL-13 pathway in macrophages. *PLoS ONE* **2018**, *13*, e0197604. [[CrossRef](#)] [[PubMed](#)]
53. Larson-Casey, J.L.; Deshane, J.S.; Ryan, A.J.; Thannickal, V.J.; Carter, A.B. Macrophage Akt1 Kinase-Mediated Mitophagy Modulates Apoptosis Resistance and Pulmonary Fibrosis. *Immunity* **2016**, *44*, 582–596. [[CrossRef](#)] [[PubMed](#)]
54. Yao, Y.; Wang, Y.; Zhang, Z.; He, L.; Zhu, J.; Zhang, M.; He, X.; Cheng, Z.; Ao, Q.; Cao, Y.; et al. Chop Deficiency Protects Mice Against Bleomycin-Induced Pulmonary Fibrosis by Attenuating M2 Macrophage Production. *Mol. Ther.* **2016**, *24*, 915–925. [[CrossRef](#)] [[PubMed](#)]
55. Wang, Y.; Zhang, L.; Wu, G.R.; Zhou, Q.; Yue, H.; Rao, L.Z.; Yuan, T.; Mo, B.; Wang, F.X.; Chen, L.M.; et al. MBD2 serves as a viable target against pulmonary fibrosis by inhibiting macrophage M2 program. *Sci. Adv.* **2021**, *7*, eabb6075. [[CrossRef](#)] [[PubMed](#)]
56. He, J.; Du, Y.; Li, G.; Xiao, P.; Sun, X.; Song, W.; Lai, L.; Xia, M.; Zhang, J.; Wang, Q. Myeloid Fbxw7 Prevents Pulmonary Fibrosis by Suppressing TGF- $\beta$  Production. *Front. Immunol.* **2021**, *12*, 760138. [[CrossRef](#)] [[PubMed](#)]
57. Huo, R.; Guo, Q.; Hu, J.; Li, N.; Gao, R.; Mi, L.; Zhang, Z.; Liu, H.; Guo, Z.; Zhao, H.; et al. Therapeutic Potential of Janus Kinase Inhibitors for the Management of Interstitial Lung Disease. *Drug Des. Dev. Ther.* **2022**, *16*, 991–998. [[CrossRef](#)]
58. Fan, X.; Wang, Z. STAT1 antisense oligonucleotides attenuate the proinflammatory cytokine release of alveolar macrophages in bleomycin-induced fibrosis. *Cell Mol. Immunol.* **2005**, *2*, 211–217.
59. Le, T.K.; Paris, C.; Khan, K.S.; Robson, F.; Ng, W.L.; Rocchi, P. Nucleic Acid-Based Technologies Targeting Coronaviruses. *Trends Biochem. Sci.* **2021**, *46*, 351–365. [[CrossRef](#)]
60. Nakazawa, Y.; Ohtsuka, S.; Nakahashi-Oda, C.; Shibuya, A. Cutting Edge: Involvement of the Immunoreceptor CD300c2 on Alveolar Macrophages in Bleomycin-Induced Lung Fibrosis. *J. Immunol.* **2019**, *203*, 3107–3111. [[CrossRef](#)]
61. Cardoneanu, A.; Burlui, A.M.; Macovei, L.A.; Bratou, I.; Richter, P.; Rezus, E. Targeting Systemic Sclerosis from Pathogenic Mechanisms to Clinical Manifestations: Why IL-6? *Biomedicines* **2022**, *10*, 318. [[CrossRef](#)]
62. Sun, N.N.; Zhang, Y.; Huang, W.H.; Zheng, B.J.; Jin, S.Y.; Li, X.; Meng, Y. Macrophage exosomes transfer angiotensin II type 1 receptor to lung fibroblasts mediating bleomycin-induced pulmonary fibrosis. *Chin. Med. J.* **2021**, *134*, 2175–2185. [[CrossRef](#)]
63. Chen, Y.; Hao, X.; Li, M.; Tian, Z.; Cheng, M. UGRP1-modulated MARCO+ alveolar macrophages contribute to age-related lung fibrosis. *Immun. Ageing* **2023**, *20*, 14. [[CrossRef](#)]
64. Durairaj, P.; Venkatesan, S.; Narayanan, V.; Babu, M. Protective effects of curcumin on bleomycin-induced changes in lung glycoproteins. *Mol. Cell Biochem.* **2020**, *469*, 159–167. [[CrossRef](#)]
65. Suka, M.; Kido, T.; Yoshioka, W.; Hachisuka, E.; Okoshi, H.; Yamauchi, T.; Hano, H.; Okano, T.; Yokoyama, M.; Yanagisawa, H. Single intratracheal administration of cross-linked water-soluble acrylic acid polymer causes acute alveolo-interstitial inflammation and the subsequent fibrotic formation possibly via the TGF- $\beta$ 1 pathway in the lung of rats. *Toxicology* **2021**, *448*, 152647. [[CrossRef](#)]



66. Sciacchitano, S.; Lavra, L.; Morgante, A.; Olivieri, A.; Magi, F.; De Francesco, G.P.; Bellotti, C.; Salehi, L.B.; Ricci, A. Galectin-3: One Molecule for an Alphabet of Diseases, from A to Z. *Int. J. Mol. Sci.* **2018**, *19*, 379. [CrossRef]
67. Wang, Z.; Li, W.; Guo, Q.; Wang, Y.; Ma, L.; Zhang, X. Insulin-Like Growth Factor-1 Signaling in Lung Development and Inflammatory Lung Diseases. *Biomed. Res. Int.* **2018**, *2018*, 6057589. [CrossRef]
68. Artlett, C.M. The Mechanism and Regulation of the NLRP3 Inflammasome during Fibrosis. *Biomolecules* **2022**, *12*, 634. [CrossRef]
69. Ogawa, T.; Shichino, S.; Ueha, S.; Matsushima, K. Macrophages in lung fibrosis. *Int. Immunol.* **2021**, *33*, 665–671. [CrossRef]
70. Liu, G.; Zhai, H.; Zhang, T.; Li, S.; Li, N.; Chen, J.; Gu, M.; Qin, Z.; Liu, X. New therapeutic strategies for IPF: Based on the “phagocytosis-secretion-immunization” network regulation mechanism of pulmonary macrophages. *Biomed. Pharmacother.* **2019**, *118*, 109230. [CrossRef]
71. Ramírez-Hernández, A.A.; Velázquez-Enríquez, J.M.; Santos-Álvarez, J.C.; López-Martínez, A.; Reyes-Jiménez, E.; Carrasco-Torres, G.; González-García, K.; Vásquez-Garzón, V.R.; Baltierrez-Hoyos, R. The Role of Extracellular Vesicles in Idiopathic Pulmonary Fibrosis Progression: An Approach on Their Therapeutics Potential. *Cells* **2022**, *11*, 630. [CrossRef] [PubMed]
72. Yao, M.Y.; Zhang, W.H.; Ma, W.T.; Liu, Q.H.; Xing, L.H.; Zhao, G.F. microRNA-328 in exosomes derived from M2 macrophages exerts a promotive effect on the progression of pulmonary fibrosis via FAM13A in a rat model. *Exp. Mol. Med.* **2019**, *51*, 1–16. [CrossRef] [PubMed]
73. Gao, R.; Peng, X.; Perry, C.; Sun, H.; Ntokou, A.; Ryu, C.; Gomez, J.L.; Reeves, B.C.; Walia, A.; Kaminski, N.; et al. Macrophage-derived netrin-1 drives adrenergic nerve-associated lung fibrosis. *J. Clin. Investig.* **2021**, *131*, e136542. [CrossRef] [PubMed]
74. Gu, Y.; Lawrence, T.; Mohamed, R.; Liang, Y.; Yahaya, B.H. The emerging roles of interstitial macrophages in pulmonary fibrosis: A perspective from scRNA-seq analyses. *Front. Immunol.* **2022**, *13*, 923235. [CrossRef]
75. Zhang, W.; Ohno, S.; Steer, B.; Klee, S.; Staab-Weijnitz, C.A.; Wagner, D.; Lehmann, M.; Stoeger, T.; Königshoff, M.; Adler, H. S100a4 Is Secreted by Alternatively Activated Alveolar Macrophages and Promotes Activation of Lung Fibroblasts in Pulmonary Fibrosis. *Front. Immunol.* **2018**, *9*, 1216. [CrossRef]
76. Singh, A.; Chakraborty, S.; Wong, S.W.; Hefner, N.A.; Stuart, A.; Qadir, A.S.; Mukhopadhyay, A.; Bachmaier, K.; Shin, J.W.; Rehman, J.; et al. Nanoparticle targeting of de novo profibrotic macrophages mitigates lung fibrosis. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2121098119. [CrossRef]
77. Han, S.; Lu, Q.; Liu, X. Advances in cellular senescence in idiopathic pulmonary fibrosis (Review). *Exp. Ther. Med.* **2023**, *25*, 145. [CrossRef]
78. Hou, J.; Shi, J.; Chen, L.; Lv, Z.; Chen, X.; Cao, H.; Xiang, Z.; Han, X. M2 macrophages promote myofibroblast differentiation of LR-MSCs and are associated with pulmonary fibrogenesis. *Cell Commun. Signal.* **2018**, *16*, 89. [CrossRef]
79. Sennello, J.A.; Misharin, A.V.; Flozak, A.S.; Berdnikovs, S.; Cheresch, P.; Varga, J.; Kamp, D.W.; Budinger, G.R.; Gottardi, C.J.; Lam, A.P. Lrp5/ $\beta$ -Catenin Signaling Controls Lung Macrophage Differentiation and Inhibits Resolution of Fibrosis. *Am. J. Respir. Cell Mol. Biol.* **2017**, *56*, 191–201. [CrossRef]
80. Glass, D.S.; Grossfeld, D.; Renna, H.A.; Agarwala, P.; Spiegler, P.; DeLeon, J.; Reiss, A.B. Idiopathic pulmonary fibrosis: Current and future treatment. *Clin. Respir. J.* **2022**, *16*, 84–96. [CrossRef]
81. Maghsadi, Z.; Azadmehr, A.; Moghadamnia, A.A.; Feizi, F.; Hamidi, N. N-Acetylcysteine attenuated pulmonary fibrosis induced by bleomycin. *Res. Pharm. Sci.* **2023**, *18*, 177–184.
82. Guiot, J.; Cambier, M.; Boeckx, A.; Henket, M.; Nivelles, O.; Gester, F.; Louis, E.; Malaise, M.; Dequiedt, F.; Louis, R.; et al. Macrophage-derived exosomes attenuate fibrosis in airway epithelial cells through delivery of antifibrotic miR-142-3p. *Thorax* **2020**, *75*, 870–881. [CrossRef]
83. Enomoto, Y.; Suzuki, Y.; Hozumi, H.; Mori, K.; Kono, M.; Karayama, M.; Furuhashi, K.; Fujisawa, T.; Enomoto, N.; Nakamura, Y.; et al. Clinical significance of soluble CD163 in polymyositis-related or dermatomyositis-related interstitial lung disease. *Arthritis Res. Ther.* **2017**, *19*, 9. [CrossRef]
84. Horiike, Y.; Suzuki, Y.; Fujisawa, T.; Yasui, H.; Karayama, M.; Hozumi, H.; Furuhashi, K.; Enomoto, N.; Nakamura, Y.; Inui, N.; et al. Successful classification of macrophage-mannose receptor CD206 in severity of anti-MDA5 antibody positive dermatomyositis associated ILD. *Rheumatology* **2019**, *58*, 2143–2152. [CrossRef]
85. Ye, L.; Zuo, Y.; Chen, F.; Xu, Y.; Zhang, P.; Yang, H.; Lin, S.; Peng, Q.; Wang, G.; Shu, X. Resistin Expression Is Associated with Interstitial Lung Disease in Dermatomyositis. *Front. Med.* **2022**, *9*, 903887. [CrossRef]
86. Matsuda, S.; Kotani, T.; Kuwabara, H.; Suzuka, T.; Kiboshi, T.; Wada, Y.; Ishida, T.; Fujiki, Y.; Shiba, H.; Hata, K.; et al. Association of M2 macrophages, Th2, and B cells with pathomechanism in microscopic polyangiitis complicated by interstitial lung disease. *J. Rheumatol.* **2022**, *49*, 913–921. [CrossRef]
87. Matsuda, S.; Kotani, T.; Kuwabara, H.; Suzuka, T.; Kiboshi, T.; Fukui, K.; Ishida, T.; Fujiki, Y.; Shiba, H.; Hata, K.; et al. CCL2 produced by CD68+/CD163+ macrophages as a promising clinical biomarker of microscopic polyangiitis-interstitial lung disease. *Rheumatology* **2021**, *60*, 4643–4653. [CrossRef]
88. Gaurav, R.; Mikuls, T.R.; Thiele, G.M.; Nelson, A.J.; Niu, M.; Guda, C.; Eudy, J.D.; Barry, A.E.; Wyatt, T.A.; Romberger, D.J.; et al. High-throughput analysis of lung immune cells in a combined murine model of agriculture dust-triggered airway inflammation with rheumatoid arthritis. *PLoS ONE* **2021**, *16*, e0240707. [CrossRef]
89. Shiomi, A.; Usui, T.; Ishikawa, Y.; Shimizu, M.; Murakami, K.; Mimori, T. GM-CSF but not IL-17 is critical for the development of severe interstitial lung disease in SKG mice. *J. Immunol.* **2014**, *193*, 849–859. [CrossRef]

90. Tsoyi, K.; Esposito, A.J.; Sun, B.; Bowen, R.G.; Xiong, K.; Poli, F.; Cardenas, R.; Chu, S.G.; Liang, X.; Ryter, S.W.; et al. Syndecan-2 regulates PAD2 to exert antifibrotic effects on RA-ILD fibroblasts. *Sci. Rep.* **2022**, *12*, 2847. [[CrossRef](#)]
91. Xiong, L.; Ye, H.; Ma, W.L. Animal models of rheumatoid arthritis-associated interstitial lung disease. *Immun. Inflamm. Dis.* **2021**, *9*, 37–47. [[CrossRef](#)] [[PubMed](#)]
92. Wu, E.K.; Henkes, Z.I.; McGowan, B.; Bell, R.D.; Velez, M.J.; Livingstone, A.M.; Ritchlin, C.T.; Schwarz, E.M.; Rahimi, H. TNF-Induced Interstitial Lung Disease in a Murine Arthritis Model: Accumulation of Activated Monocytes, Conventional Dendritic Cells, and CD21+/CD23– B Cell Follicles Is Prevented with Anti-TNF Therapy. *J. Immunol.* **2019**, *203*, 2837–2849. [[CrossRef](#)] [[PubMed](#)]
93. Rudnik, M.; Hukara, A.; Kocherova, I.; Jordan, S.; Schniering, J.; Milleret, V.; Ehrbar, M.; Klingel, K.; Feghali-Bostwick, C.; Distler, O.; et al. Elevated Fibronectin Levels in Profibrotic CD14+ Monocytes and CD14+ Macrophages in Systemic Sclerosis. *Front. Immunol.* **2021**, *12*, 642891. [[CrossRef](#)] [[PubMed](#)]
94. Gao, X.; Jia, G.; Guttman, A.; DePianto, D.J.; Morshead, K.B.; Sun, K.H.; Ramamoorthi, N.; Vander Heiden, J.A.; Modrusan, Z.; Wolters, P.J.; et al. Osteopontin Links Myeloid Activation and Disease Progression in Systemic Sclerosis. *Cell Rep. Med.* **2020**, *1*, 100140. [[CrossRef](#)]
95. Sun, C.; Chen, S.Y. RGC32 Promotes Bleomycin-Induced Systemic Sclerosis in a Murine Disease Model by Modulating Classically Activated Macrophage Function. *J. Immunol.* **2018**, *200*, 2777–2785. [[CrossRef](#)]
96. Bonhomme, O.; André, B.; Gester, F.; de Seny, D.; Moermans, C.; Struman, I.; Louis, R.; Malaise, M.; Guiot, J. Biomarkers in systemic sclerosis-associated interstitial lung disease: Review of the literature. *Rheumatology* **2019**, *58*, 1534–1546. [[CrossRef](#)]
97. Li, D.; Guabiraba, R.; Besnard, A.G.; Komai-Koma, M.; Jabir, M.S.; Zhang, L.; Graham, G.J.; Kurowska-Stolarska, M.; Liew, F.Y.; McSharry, C.; et al. IL-33 promotes ST2-dependent lung fibrosis by the induction of alternatively activated macrophages and innate lymphoid cells in mice. *J. Allergy Clin. Immunol.* **2014**, *134*, 1422–1432.e11. [[CrossRef](#)]
98. Li, S.; Gao, S.; Jiang, Q.; Liang, Q.; Luan, J.; Zhang, R.; Zhang, F.; Ruan, H.; Li, X.; Zhou, H.; et al. Clevudine attenuates bleomycin-induced early pulmonary fibrosis via regulating M2 macrophage polarization. *Int. Immunopharmacol.* **2021**, *101*, 108271. [[CrossRef](#)]
99. Nakagome, K.; Dohi, M.; Okunishi, K.; Tanaka, R.; Miyazaki, J.; Yamamoto, K. In Vivo IL-10 gene delivery attenuates bleomycin induced pulmonary fibrosis by inhibiting the production and activation of TGF-beta in the lung. *Thorax* **2006**, *61*, 886–894. [[CrossRef](#)]
100. El-Demerdash, E. Anti-inflammatory and antifibrotic effects of methyl palmitate. *Toxicol. Appl. Pharmacol.* **2011**, *254*, 238–244. [[CrossRef](#)]
101. Wang, J.; Xu, L.; Xiang, Z.; Ren, Y.; Zheng, X.; Zhao, Q.; Zhou, Q.; Zhou, Y.; Wang, Y. Microcystin-LR ameliorates pulmonary fibrosis via modulating CD206+ M2-like macrophage polarization. *Cell Death Dis.* **2020**, *11*, 136. [[CrossRef](#)]
102. Huang, J.; Maier, C.; Zhang, Y.; Soare, A.; Dees, C.; Beyer, C.; Harre, U.; Chen, C.W.; Distler, O.; Schett, G.; et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. *Ann. Rheum. Dis.* **2017**, *76*, 1941–1948. [[CrossRef](#)]
103. Toda, M.; Mizuguchi, S.; Minamiyama, Y.; Yamamoto-Oka, H.; Aota, T.; Kubo, S.; Nishiyama, N.; Shibata, T.; Takemura, S. Pirfenidone suppresses polarization to M2 phenotype macrophages and the fibrogenic activity of rat lung fibroblasts. *J. Clin. Biochem. Nutr.* **2018**, *63*, 58–65. [[CrossRef](#)]
104. Okazaki, H.; Sato, S.; Koyama, K.; Morizumi, S.; Abe, S.; Azuma, M.; Chen, Y.; Goto, H.; Aono, Y.; Ogawa, H.; et al. The novel inhibitor PRI-724 for Wnt/ $\beta$ -catenin/CBP signaling ameliorates bleomycin-induced pulmonary fibrosis in mice. *Exp. Lung Res.* **2019**, *45*, 188–199. [[CrossRef](#)]
105. Raghu, G.; Hamblin, M.J.; Brown, A.W.; Golden, J.A.; Ho, L.A.; Wijsenbeek, M.S.; Vasakova, M.; Pesci, A.; Antin-Ozerkis, D.E.; Meyer, K.C.; et al. Long-term evaluation of the safety and efficacy of recombinant human pentraxin-2 (rhPTX-2) in patients with idiopathic pulmonary fibrosis (IPF): An open-label extension study. *Respir. Res.* **2022**, *23*, 129. [[CrossRef](#)]
106. Guo, Z.; Li, S.; Zhang, N.; Kang, Q.; Zhai, H. Schisandra Inhibit Bleomycin-Induced Idiopathic Pulmonary Fibrosis in Rats via Suppressing M2 Macrophage Polarization. *Biomed. Res. Int.* **2020**, *2020*, 5137349. [[CrossRef](#)]
107. Lescoat, A.; Lelong, M.; Jeljeli, M.; Piquet-Pellorce, C.; Morzadec, C.; Ballerie, A.; Jouneau, S.; Jegou, P.; Vernhet, L.; Batteux, F.; et al. Combined anti-fibrotic and anti-inflammatory properties of JAK-inhibitors on macrophages in vitro and in vivo: Perspectives for scleroderma-associated interstitial lung disease. *Biochem. Pharmacol.* **2020**, *178*, 114103. [[CrossRef](#)]
108. Liu, B.; Jiang, Q.; Chen, R.; Gao, S.; Xia, Q.; Zhu, J.; Zhang, F.; Shao, C.; Liu, X.; Li, X.; et al. Tacrolimus ameliorates bleomycin-induced pulmonary fibrosis by inhibiting M2 macrophage polarization via JAK2/STAT3 signaling. *Int. Immunopharmacol.* **2022**, *113*, 109424. [[CrossRef](#)]
109. Boutel, M.; Boutou, A.; Pitsiou, G.; Garyfallos, A.; Dimitroulas, T. Efficacy and Safety of Nintedanib in Patients with Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD): A Real-World Single Center Experience. *Diagnostics* **2023**, *13*, 1221. [[CrossRef](#)]
110. Kamenova, A.; Tzouveleki, A.; Margaritopoulos, G.A. Recent advances in the treatment of systemic sclerosis associated interstitial lung disease. *Front. Med.* **2023**, *10*, 1155771. [[CrossRef](#)]
111. Tardella, M.; Di Carlo, M.; Carotti, M.; Giovagnoni, A.; Salaffi, F. Abatacept in rheumatoid arthritis-associated interstitial lung disease: Short-term outcomes and predictors of progression. *Clin. Rheumatol.* **2021**, *40*, 4861–4867. [[CrossRef](#)] [[PubMed](#)]

112. Khanna, D.; Tashkin, D.P.; Wells, A.U.; Seibold, J.R.; Wax, S.; Vazquez-Mateo, C.; Fleuranceau-Morel, P.; Damian, D.; Denton, C.P. STRATUS: A Phase II Study of Abituzumab in Patients With Systemic Sclerosis-associated Interstitial Lung Disease. *J. Rheumatol.* **2021**, *48*, 1295–1298. [[CrossRef](#)]
113. Li Wilkinson, M.G.; Deakin, C.T.; Papadopoulou, C.; Eleftheriou, D.; Wedderburn, L.R. JAK inhibitors: A potential treatment for JDM in the context of the role of interferon-driven pathology. *Pediatr. Rheumatol. Online J.* **2021**, *19*, 146. [[CrossRef](#)] [[PubMed](#)]
114. Mwangi, J.; Litteken, C.; Gorthi, R.; Attoti, Y.; Atluri, R. Belimumab in the Treatment of Connective Tissue Disease-Associated Interstitial Lung Disease: Case Report and Literature Review. *Cureus* **2021**, *13*, e19218. [[CrossRef](#)] [[PubMed](#)]
115. Penke, L.R.K.; Speth, J.; Wettlaufer, S.; Draijer, C.; Peters-Golden, M. Bortezomib Inhibits Lung Fibrosis and Fibroblast Activation without Proteasome Inhibition. *Am. J. Respir. Cell Mol. Biol.* **2022**, *66*, 23–37. [[CrossRef](#)]
116. Giacomelli, R.; Liakouli, V.; Berardicurti, O.; Ruscitti, P.; Di Benedetto, P.; Carubbi, F.; Guggino, G.; Di Bartolomeo, S.; Ciccia, F.; Triolo, G.; et al. Interstitial lung disease in systemic sclerosis: Current and future treatment. *Rheumatol. Int.* **2017**, *37*, 853–863. [[CrossRef](#)]
117. Harari, S.; Wells, A.U.; Wuyts, W.A.; Nathan, S.D.; Kirchgaessler, K.U.; Bengus, M.; Behr, J. The 6-min walk test as a primary end-point in interstitial lung disease. *Eur. Respir. Rev.* **2022**, *31*, 220087. [[CrossRef](#)]
118. Vonk, M.C. Is there still a role for cyclophosphamide in the treatment of systemic sclerosis? *J. Scleroderma Relat. Disord.* **2021**, *6*, 117–122. [[CrossRef](#)]
119. Kim, G.H.J.; Tashkin, D.P.; Lo, P.; Brown, M.S.; Volkmann, E.R.; Gjertson, D.W.; Khanna, D.; Elashoff, R.M.; Tseng, C.H.; Roth, M.D.; et al. Using Transitional Changes on High-Resolution Computed Tomography to Monitor the Impact of Cyclophosphamide or Mycophenolate Mofetil on Systemic Sclerosis-Related Interstitial Lung Disease. *Arthritis Rheumatol.* **2020**, *72*, 316–325. [[CrossRef](#)]
120. Eapen, M.S.; Gaikwad, A.V.; Thompson, I.E.; Lu, W.; Myers, S.; Sharma, P.; Sohal, S.S. The effectiveness of immunosuppressive cyclosporin in attenuating the progression of interstitial lung diseases. *J. Thorac. Dis.* **2019**, *11*, S1139–S1142. [[CrossRef](#)]
121. Chen, I.C.; Liu, Y.C.; Wu, Y.H.; Lo, S.H.; Dai, Z.K.; Hsu, J.H.; Tseng, Y.H. Evaluation of Proteasome Inhibitors in the Treatment of Idiopathic Pulmonary Fibrosis. *Cells* **2022**, *11*, 1543. [[CrossRef](#)]
122. Assassi, S.; Volkmann, E.R.; Zheng, W.J.; Wang, X.; Wilhalme, H.; Lyons, M.A.; Roth, M.D.; Tashkin, D.P. Peripheral blood gene expression profiling shows predictive significance for response to mycophenolate in systemic sclerosis-related interstitial lung disease. *Ann. Rheum. Dis.* **2022**, *81*, 854–860. [[CrossRef](#)]
123. Naidu, G.S.R.S.; Sharma, S.K.; Adarsh, M.B.; Dhir, V.; Sinha, A.; Dhooria, S.; Jain, S. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: A double-blind, placebo-controlled, randomized trial. *Rheumatol. Int.* **2020**, *40*, 207–216. [[CrossRef](#)]
124. Kulshrestha, R.; Pandey, A.; Jaggi, A.; Bansal, S. Beneficial effects of N-acetylcysteine on protease-antiprotease balance in attenuating bleomycin-induced pulmonary fibrosis in rats. *Iran. J. Basic. Med. Sci.* **2020**, *23*, 396–405.
125. Denton, C.P.; Goh, N.S.; Humphries, S.M.; Maher, T.M.; Spiera, R.; Devaraj, A.; Ho, L.; Stock, C.; Erhardt, E.; Alves, M.; et al. Extent of fibrosis and lung function decline in patients with systemic sclerosis and interstitial lung disease: Data from the SENSICIS trial. *Rheumatology* **2023**, *62*, 1870–1876. [[CrossRef](#)] [[PubMed](#)]
126. Solomon, J.J.; Danoff, S.K.; Woodhead, F.A.; Hurwitz, S.; Maurer, R.; Glaspole, I.; Dellaripa, P.F.; Gooptu, B.; Vassallo, R.; Cox, P.G.; et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: A randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir. Med.* **2023**, *11*, 87–96. [[CrossRef](#)]
127. Hsu, V.M.; Denton, C.P.; Domsic, R.T.; Furst, D.E.; Rischmueller, M.; Stanislav, M.; Steen, V.D.; Distler, J.H.W.; Korish, S.; Cooper, A.; et al. Pomalidomide in Patients with Interstitial Lung Disease due to Systemic Sclerosis: A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study. *J. Rheumatol.* **2018**, *45*, 405–410. [[CrossRef](#)]
128. Available online: <https://www.prometheusbiosciences.com/pipeline/pr023/tl1a/> (accessed on 30 March 2023).
129. Maher, T.M.; Tudor, V.A.; Saunders, P.; Gibbons, M.A.; Fletcher, S.V.; Denton, C.P.; Hoyles, R.K.; Parfrey, H.; Renzoni, E.A.; Kokosi, M.; et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): A double-blind, double-dummy, randomised, controlled, phase 2b trial. *Lancet Respir. Med.* **2023**, *11*, 45–54. [[CrossRef](#)]
130. Takada, K.; Katada, Y.; Ito, S.; Hayashi, T.; Kishi, J.; Itoh, K.; Yamashita, H.; Hirakata, M.; Kawahata, K.; Kawakami, A.; et al. Impact of adding tacrolimus to initial treatment of interstitial pneumonitis in polymyositis/dermatomyositis: A single-arm clinical trial. *Rheumatology* **2020**, *59*, 1084–1093. [[CrossRef](#)]
131. Kuwana, M.; Wakasugi, N.; Furuya, T.; Uno, S.; Suda, T. Tacrolimus in Patients With Interstitial Pneumonia Associated With Polymyositis or Dermatomyositis: Interim Report of Postmarketing Surveillance in Japan. *J. Rheumatol.* **2022**, *49*, 707–718. [[CrossRef](#)]
132. Mansour, S.M.; El-Abhar, H.S.; Soubh, A.A. MiR-200a inversely correlates with Hedgehog and TGF- $\beta$  canonical/non-canonical trajectories to orchestrate the anti-fibrotic effect of Tadalafil in a bleomycin-induced pulmonary fibrosis model. *Inflammopharmacology* **2021**, *29*, 167–182. [[CrossRef](#)] [[PubMed](#)]
133. Parida, J.; Nath, A.; Neyaz, Z.; Agarwal, V. A double blind randomized control trial of oral tadalafil in interstitial lung disease of scleroderma [abstract]. *Arthritis Rheum.* **2014**, *66*, S739.
134. Kalyoncu, U.; Bilgin, E.; Erden, A.; Satış, H.; Tufan, A.; Tekgöz, E.; Ateş, A.; Coşkun, B.N.; Yağız, B.; Küçükşahin, O.; et al. Efficacy and safety of tofacitinib in rheumatoid arthritis-associated interstitial lung disease: TReasure real-life data. *Clin. Exp. Rheumatol.* **2022**, *40*, 2071–2077. [[PubMed](#)]

135. Harrison, C. Itch receptor OSMR attracts industry. *Nat. Biotechnol.* **2022**, *40*, 1306. [[CrossRef](#)]
136. Yaseen, B.; Lopez, H.; Taki, Z.; Zafar, S.; Rosario, H.; Abdi, B.A.; Vigneswaran, S.; Xing, F.; Arumalla, N.; Black, S.; et al. Interleukin-31 promotes pathogenic mechanisms underlying skin and lung fibrosis in scleroderma. *Rheumatology* **2020**, *59*, 2625–2636. [[CrossRef](#)]
137. Erre, G.L.; Sebastiani, M.; Manfredi, A.; Gerratana, E.; Atzeni, F.; Passiu, G.; Mangoni, A.A. Antifibrotic drugs in connective tissue disease-related interstitial lung disease (CTD-ILD): From mechanistic insights to therapeutic applications. *Drugs Context* **2021**, *10*, 2020-8-6. [[CrossRef](#)]
138. Faust, A.; Bäumer, N.; Schlütermann, A.; Becht, M.; Greune, L.; Geyer, C.; Rüter, C.; Margeta, R.; Wittmann, L.; Dersch, P.; et al. Tumor-Cell-Specific Targeting of Ibrutinib: Introducing Electrostatic Antibody-Inhibitor Conjugates (AiCs). *Angew. Chem. Int. Ed. Engl.* **2022**, *61*, e202109769. [[CrossRef](#)]
139. Gearty, S.V.; Dündar, F.; Zumbo, P.; Espinosa-Carrasco, G.; Shakiba, M.; Sanchez-Rivera, F.J.; Socci, N.D.; Trivedi, P.; Lowe, S.W.; Lauer, P.; et al. An autoimmune stem-like CD8 T cell population drives type 1 diabetes. *Nature* **2022**, *602*, 156–161. [[CrossRef](#)]
140. Nie, Y.; Zhao, L.; Zhang, X. B Cell Aberrance in Lupus: The Ringleader and the Solution. *Clin. Rev. Allergy Immunol.* **2022**, *62*, 301–323. [[CrossRef](#)]
141. Bohdziewicz, A.; Pawlik, K.K.; Maciejewska, M.; Sikora, M.; Alda-Malicka, R.; Czuwara, J.; Rudnicka, L. Future Treatment Options in Systemic Sclerosis-Potential Targets and Ongoing Clinical Trials. *J. Clin. Med.* **2022**, *11*, 1310. [[CrossRef](#)]
142. Radziszewska, A.; Moulder, Z.; Jury, E.C.; Ciurtin, C. CD8+ T Cell Phenotype and Function in Childhood and Adult-Onset Connective Tissue Disease. *Int. J. Mol. Sci.* **2022**, *23*, 11431. [[CrossRef](#)]
143. Xu, L.; Wang, F.; Luo, F. Rituximab for the treatment of connective tissue disease-associated interstitial lung disease: A systematic review and meta-analysis. *Front. Pharmacol.* **2022**, *13*, 1019915. [[CrossRef](#)]
144. Bellan, M.; Patrucco, F.; Barone-Adesi, F.; Gavelli, F.; Castello, L.M.; Nerviani, A.; Andreoli, L.; Cavagna, L.; Pirisi, M.; Sainaghi, P.P. Targeting CD20 in the treatment of interstitial lung diseases related to connective tissue diseases: A systematic review. *Autoimmun. Rev.* **2020**, *19*, 102453. [[CrossRef](#)]

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.