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Role of Macrophage in Pathogenesis of Pulmonary Fibrosis: A Review

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Abstract

Pulmonary fibrosis is a severe disease that involves the lung parenchyma. The pattern of the disease progresses with increasing fibrosis, resulting in severe restrictive lung disease. Also, revealed that each patient normally has a median survival rate of 2 to 5 years after a diagnosis. Having said that, current treatment options focus on only alleviating the symptoms and trying to stabilise or reverse their progression, and no cure can be seen on the horizon. Some natural immunity elements play a role in the development of pulmonary fibrosis, and macrophages are among them. At first, they prevent lung injury by encouraging inflammation and attracting immune cells. However, prolonged, persistent activation has the paradoxical effect of preventing the clearance of inflammatory mediators and prolonging inflammation. This, in turn, activates the mediator-producing molecules that will lead to remodelling and fibrosis. Current investigations show that macrophages have phenotypic versatility and can enhance tissue remodelling or fibrosis, so pulmonary fibrosis may be exploited by targeting macrophages. In this review, we propose the functions of macrophages in pulmonary fibrosis: Considering polarity, activity control factors, macrophage to other cell types, and signalling networks. The issue of the potential of advertised opportunities in modulating macrophage polarisation and the developments related to the non-coding RNA drugs are also considered. Last of all, special attention should be paid to the enhancement of the investigations concerning macrophages within this disease and on experiments with different therapies for pulmonary fibrosis.

Keywords

Pulmonary Fibrosis, Macrophages, Polarization, M1 Macrophages, Lung Cancer, Lung Architecture

1. Introduction

Pulmonary fibrosis is a severe disabling respiratory condition involving the gradual thickening of the lung tissue and causing a significant reduction in lung function and people's quality of life. As of 2020, this disease affects millions of people, and its rate varies depending on the population group or geographical location, making it a significant public health concern [1]. Moreover, Pulmonary fibrosis has multiple causes, including environmental factors and idiopathic causes, and seeing that multiple factors precipitate it, it is a complex disease to diagnose and treat effectively as well. Macrophages are pivotal cells of innate immunity and are now being acknowledged to participate in different aspects of the pathophysiology of pulmonary fibrosis [2]. These cells have good plasticity, transforming them into different activation states that allow them to respond to diverse signals [3]. About pulmonary fibrosis, macrophages can be resolution-promoting cells or pathogenic in that they support and perpetuate fibrosis by elaborating cytokines and growth factors [4] [5]. Future work needs to explore the underlying mechanism of macrophages in pulmonary fibrosis to find more effective treatment strategies. Indeed, in fibrosis, macrophages play a crucial role in dynamic switching between different phenotypes depending on soluble factors and interaction with other cell types, including epithelial cells and fibroblasts [6] [7]. Through analysis of such multifaceted processes, the investigators may identify one or several links targeted to stop or reverse fibrosis, giving a new chance for those enemies of this deadly disease—the patient [8]. The objectives of this review include facets of macrophage mechanisms in pulmonary fibrosis, factors that modulate macrophage function, interactions with other cell types, and signalling pathways [9].

2. Polarization of Macrophage

Macrophage polarization is a general phenomenon in the immune system whereby heterogeneous white blood cell macrophages change their functionality depending on the prevailing stimuli. This enables them to play several functions in shielding the body and fixing tissue [10]. Depending upon their activation, macrophages are classified into M1 and M2 polarizations, each having peculiar properties [11].

2.1. M1 Polarization

M1 macrophages, or the classically activated type of macrophages, are part of these multifunctional cells central to an organism's protection system, especially in situations involving pathogenic invasions and inflammation [12]. These cells are usually associated with inflammation and commonly stimulated by cytokines, particularly IFN-γ and microbial component-LPS. When ignited, M1 macrophages possess potent candidacidal and neoplastic activity; they produce many cytokines, such as IL-1, IL-6, IL-12, and TNF-α [13]. They also release reactive oxygen species (ROS) and nitric oxide (NO), which are strong bacteria eliminators. The primary role of M1 macrophage is to make the environment unfriendly for any

invading pathogen, support the efforts of the immune responses, and encourage inflammation. However, chronic activation of M1 macrophages results in an uncontrolled and destructive inflammation that can be associated with various diseases—autoimmune diseases and certain types of cancer. The drawback of this situation is that M1 macrophages are essential for the early stage of the immune response, as they touch both innate and adaptive immunity and make the basis for further healing and tissue repair [14].

2.2. M2 Polarization

M2 macrophages are specific subsets of antigen-presenting cells involved in tissue repair and positive feedback regulation of chronically inflamed tissue [15]. While M1 macrophages are associated with the TNF-*α* and IL-"ß" productions, examples being the intracellular pathogens, M2 macrophages, unlike their counterpart, are induced by cytokines IL-4 and IL-13 produced primarily by Th2 cells. They also responded to immune complexes and other regulatory signals. It is generally accepted that M2 macrophages play anti-inflammatory functions, which are necessary to avoid exacerbating the immune processes when a recurrence of the dangers indicated by the presence of pathogens and tissue damages Topsf [16]. They release several mediators, such as interleukin 10 (IL-10) and transforming growth factor-beta (TGF-beta), and possess the property of anti-inflammatory healing. These cells play a role in events like the synthesis of the extracellular matrix, the formation of blood vessels, and wound healing. In the context of chronic inflammation, those of M2 phenotype macrophages have the potential to reduce pathogenic inflammatory reactions but also can promote tumour growth. In an environment surrounding the tumour, these cells may be utilised by the tumour as it stimulates growth, formation of blood vessels, and metastasis in an immunosuppressive environment. M2 macrophages are critical in maintaining tissue function and regulating inflammation and repair processes. These findings show that the immune system is multifaceted and stresses macrophage polarisation's role in benefit and harm [17].

Figure 1, Major differences in the functions of M1 and M2 and the types of cells involved in the inflammatory processes. It is recognized that macrophages play a significant role in immunity. They can form distinct phenotypes based on different signals in an environment. M1 and M2 are the two central polarized states of the Giant Carcharias. M1 Carcharias: Generally triggered by phrenin-γ (interferon *γ*) and lipopolysaccharide (LPS). They are considered proinflammatory because they can produce a range of inflammatory mediators such as Il-12, Il-23, Tnf-a, etc. Links with the response of Th1 cells, another kind of helper T cells, which elicited the cellular immunity.M1 type Carcharias cells are involved in connection with inflammatory response, tumor resistance, and graft rejection.M2 Carcharias usually activated by Il-4 M1 and M2 activation states and the diverse impact on biological processes. M1 cells actively participate in infections and tumor removal, while strong M1 reactions can be dangerous for tissues. In contrast, M2-type

megahertz cells execute a vital function within tissue repair and maintaining tissue homeostasis, decreasing inflammation and inciting tissue repair and remodelling.

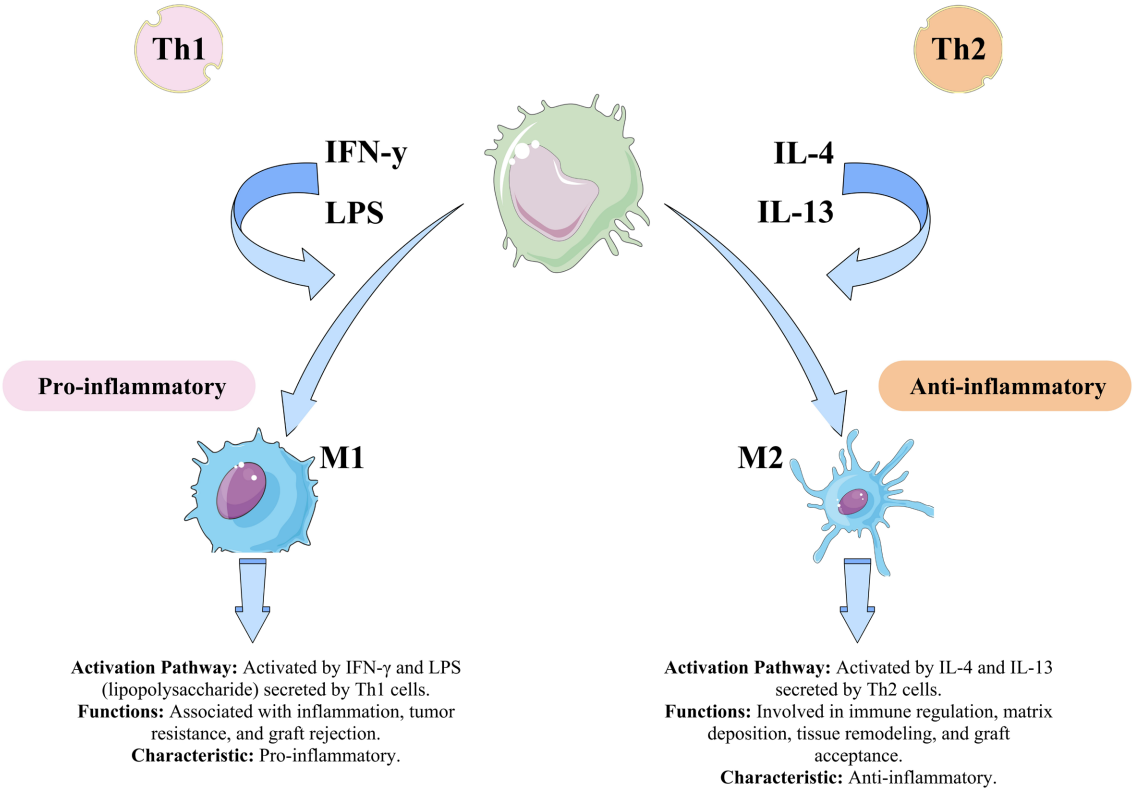

Figure 1. Major differences in the functions of M1 and M2, types of the cells involved in the inflammatory processes.

3. Critical Characteristics of M1 and M2 Macrophages

Characteristics of M1 and M2 Macrophages

Table 1, M1 macrophages and M2 macrophages, also known as alternatively activated macrophages. These two phenotypes thus have special features and roles that play crucial roles in determining immune response [18]. M1 activated macrophage by M1 activation through Interferon-gamma (IFN-γ) and Lipopolysaccharide (LPS). These macrophages are particularly characterized by their ability to be pro-inflammatory and microbicidal. The effector cells of this new model produce cytokines like Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-12 (IL-12), Tumor Necrosis Factor-alpha (TNF-α), Nitric Oxide (NO) and Reactive Oxygen Species (ROS). CDS T cell's main function in immunes is to remove pathogens and stimulate Th1 cytokines, which are very important for intracellular pathogens and particular bacteria. Data regarding the metabolic state of M1 macrophages indicates that these cells have high glycolytic rates and low levels of oxidative phosphorylation. They present inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2) MHC-II, CD80 and CD86 markers. M1 macrophages are normally located in areas of bacterial infection and Th1 disease. However, their

constant activity leads to a process of chronic inflammation and destruction of the affected tissues. On the other hand, M2 macrophages are induced by Interleukin 4 (IL-4), Interleukin 13 (IL-13) and immune complexes. These macrophages are anti-inflammatory and play a part in tissue repair. They secrete cytokines like Interleukin-10 (IL-10) and Transforming Growth factor-beta (TGF-β). It was found that M2 macrophages are extensively involved in Th2 response and tissue remodelling. It has been observed that they express a very high value for oxidative phosphorylation and lipid metabolism. They produce cytokines including Arginase-1 (Arg-1), CD 206, CD 163, Fizz1 and Ym1. M2 macrophages are usually resident in the tissues related to parasitic diseases and allergic inflammation and in the tumour microenvironment. They participate in allergic reactions, tissue healing and cancer.

Table 1. Key characteristics of M1 and M2 macrophages.

Feature	M1 Macrophages (classically activated)	M2 Macrophages (alternatively activated)
Activation stimuli	IFN-γ, LPS	IL-4, IL-13, immune complexes
Cytokines produced	IL-1, IL-6, IL-12, TNF-α, NO, ROS	IL-10, TGF-β
Function	Pro-inflammatory, microbicidal	Anti-inflammatory, tissue repair
Role in immunity	Pathogen clearance, Th1 response	Th2 response, tissue remodeling
Metabolic profile	High glycolysis, low oxidative phosphorylation	High oxidative phosphorylation, lipid metabolism
Role in disease	Can contribute to chronic inflammation and tissue damage	Involved in allergic responses, tissue repair, and tumor progression
Markers	iNOS, COX-2, MHC-II, CD80, CD86	Arg-1, CD206, CD163, Fizz1, Ym1
Typical environment	Bacterial infections, Th1-mediated diseases	Parasitic infections, allergic inflammation, tumor microenvironment

4. Factors Regulating the Polarization of Macrophage

4.1. Cytokines

Cytokines are small proteins secreted by virtually all vertebrate cells and have an essential role in cell signalling during an immune response and inflammation events. Numerous cells, including immune cells, release molecules that can affect other cells, promoting cell growth, differentiation, and activation. Cytokines are paramount in macrophage polarisation and pulmonary fibrosis [19].

4.2. Pro-Inflammatory Cytokines

Interferon-gamma (IFN-γ): Mainly produced by the T cell and natural killer cells, this cytokine plays a crucial role in inducing M1 polarisations in macrophages. It augments the cytotoxic capacity of macrophages to exterminate pathogens and initiates the T Manuscript Cell Process, encapsulating antigens to T cells. A central integrant inflames the immune response [20].

4.3. Tumor Necrosis Factor-Alpha (TNF-α)

Secreted by macrophages, T cells, and other cells, TNF-α is one of the first cytokines released into a site of inflammation. It can have several pro-inflammatory effects, such as stimulating immune cells, raising fever, and promoting apoptosis of affected cells [21]. As for pulmonary fibrosis, TNF-α plays a part in inflammatory reactions before fibrosis.

4.4. Anti-inflammatory Cytokines

Interleukin-4 (IL-4): Interleukin-4 is produced by T cells, mast cells, and basophils and is prominent for orchestrating the polarisation of the macrophage M2 phenotype. It ultimately encourages the return to normal inflammation levels and tissue restoration. This review implies that IL-4 may facilitate the M2 phenotype to support the continuation of fibrosis in pulmonary fibrosis since M2 is responsible for the deposition of extracellular matrix and tissue remodelling [22].

4.5. Interleukin-13 (IL-13)

IL-13 is secreted by Th2 cells, natural killer T cells, and mast cells. It also has many activities related to IL-4, such as inducing M2 macrophages and stimulating fibroblasts to produce collagen, which are hallmarks of fibrosis.

4.6. Non-Coding RNAs

Non-coding RNAs (lncRNAs) are RNA molecules with more than 200 nucleotides that do not code for proteins but have essential functions in gene expression and cellular processes. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) play crucial roles in macrophage activity and pulmonary fibrosis.

4.7. MicroRNAs (miRNAs)

Small non-coding RNA silences proteins by binding to target messenger RNA. MiRNAs are generally single-stranded RNA molecules with approximately 22 nucleotides in length. BOC-RIA-CXCR3-expressing cells internalise and degrade or inhibit the translation of cellular and viral nucleic acid sequences that bear complementary sequences in the 3' untranslated regions (UTRs) of target messenger RNAs (mRNAs). In the macrophages, they can participate in polarisation, activation, and cytokines secretion processes. For instance, miR-155 is canonical to support M1 macrophages and pro-inflammatory signalling; conversely, miR-223 regulates M2 macrophages that exhibit anti-inflammatory activity. Aberrant expression of miRNAs may be involved in pulmonary fibrosis by regulating macrophage function and consequently promoting a profibrotic environment.

4.8. Long Non-Coding RNAs (lncRNAs)

Transcripts longer than 200 nucleotides that fail to code for proteins are termed lncRNAs. H2AZ has a multifaceted function in gene regulation. It is involved in chromatin remodelling, RNA polymerase II transcription, post-transcriptional

regulation of gene expression, and as part of the protein-protein interactome. Depending on the macrophages, lncRNA can figure in the inflammation reaction, which also affects the differentiation and function of macrophages. For example, the function of lncRNA MALAT1 as a molecular switch that demonstrates a dual function in regulating macrophage polarisation indicates that the management of pulmonary fibrosis is associated with M1 and M2 macrophages.

5. Other Regulatory Factors

5.1. Growth Factors

They are proteins that may incite cell division, growth or differentiation. In pulmonary fibrosis, the critical role in the fibrotic process is played by cytokines growth factors that are TGF-β and PDGF, which regulate fibroblasts to synthesise basic materials like collagen and other elements of connective tissue. [23].

5.2. Hypoxia

Reduced oxygen concentration may lead to various cellular mechanisms, such as HIF activation, that, in return, interrupt normal macrophage operations and cause fibrosis development.

Metabolic Changes: This study shows that macrophages' metabolic changes, depending on the signals within their microenvironment, influence their phenotype. For instance, brand here is an example wherein glycolysis Signifies M1 macrophage activation, whereas oxidative phosphorylation is an instantiation of the M2 macrophage activation field [24]. Therefore, specific alterations in the lung microenvironment can determine the course of pulmonary fibrosis.

6. Crosstalk between Macrophage and Epithelial Cells

Both the macrophage as well as epithelial cell signalling are important to the immune response and continued tissue homeostasis. One of the components of the innate immune system is macrophages, which can release cytokines and chemokines that can severely influence the behaviour of epithelial cells. Besides, they are capable of regulating such processes as inflammation, stimulation of tissue regeneration or function of the barrier [25]. For example, TNFα and IL1β secreted by macrophages in response to tissue damage or infection induce inflammation and change the permeability of the epithelial obstacles, making it possible to have a better immune response. Epithelial cells, however, may be able to produce factors such as TGF-β and VEGF, which skew macrophages toward an M2 phenotype, one that is more tissue repair stimulating than pro-inflammatory M1 [26]. As well as performing their critical functions of bidirectional communication, macrophages help clear apoptotic cells and debris in the resolution of inflammation. In contrast, epithelial cells proliferate and migrate to replace and repair tissue integrity.

In addition, extracellular vesicles such as exosomes also extend crosstalk to the exchange of signalling molecules and genetic material between cells, ultimately

coordinating their responses. In addition to adhesion molecules facilitating direct cell-cell contact, small molecules and ions are also exchanged through gap junctions, and together, these, in turn, promote the overall coordination of immune and tissue responses. This communication dysregulation can contribute to chronic inflammation and tissue damage in different diseases (including local poisoning). Therefore, understanding the macrophage-epithelial cell interaction is essential to developing therapeutic strategies to restore normal tissue function and immune balance [27].

Critical differences between macrophages and epithelial cells

Table 2 compares macrophages and epithelial cells' activities. Macrophages are widely distributed in the body and are primarily located in tissues [28]. Like the immune cells, they are constituents of the innate immune system, phagocytosis (engulf and digest pathogens and cell debris), antigen presentation (presenting foreign materials to other immune cells), and cytokine production (secretion of signalling cells that controls immune reaction). They are central to the initial immune response to pathogens and tissue damage, which promote inflammation and orchestrate repair. In contrast, epithelial cells are structural cells lining several organs and body cavities, for example, skin, lungs, and stomach. They have a protective barrier function, keeping harmful substances and pathogens from entering the body. Epithelial cells are not just about protection; they secrete (produce such substances as mucus or enzymes), absorb (treat us to nourishment and other substances), and, in concert with other tissues, maintain homeostasis (the balance of exchange between the body and its external environment). Injury epithelial cells are essential to tissue repair and regeneration, contributing to the integrity and function of the tissues they line.

Table 2. Differences between macrophages and epithelial cells.

Characteristic	Macrophage	Epithelial cell
Cell type	White blood cell	Tissue cell
Location	Throughout the body, especially in tissues	Forming the lining of organs and body cavities
Function	Phagocytosis, antigen presentation, cytokine production	Barrier function, secretion, absorption, protection
Role in immunity	Key player in innate immunity, clearance of pathogens and cellular debris	Contributes to innate immunity through physical barrier
Response to injury	Promotes inflammation, tissue repair, and regeneration	Regulates tissue repair and regeneration, maintains homeostasis

7. Feedback Loop between Epithelial Cells and Macrophages

The macrophage and epithelial cell interaction is bidirectional, forming a feedback loop that can lead to tissue repair or worsening of the disease process. Secretion of

factors by macrophages that regulate epithelial cell behaviour are sources that affect epithelial cell growth and repair, including growth factors and cytokine [29]. But in the realm of pulmonary fibrosis, this can go awry. For example, macrophages may release profibrotic factors, such as TGF β, that can induce epithelial-mesenchymal transition (EMT), whereby epithelial cells lose their normal phenotype and acquire a more fibroblast-like, migratory, and invasive character. It also causes the accumulation of fibroblasts and the deposition of extracellular matrix components to aid the fibrotic process [30].

On the other hand, epithelial cells can also shape macrophages. For example, epithelial cells can release anti-inflammatory cytokines or other signals to induce an M2 macrophage phenotype linked with tissue remodelling and fibrosis resolution. For instance, we found that while this regulatory mechanism should be in place in chronic conditions like pulmonary fibrosis, it can be overwhelmed, resulting in persistent activation of M1 macrophages and a fibrotic environment.

8. Involved Signaling Pathways

Since the pathogenesis of pulmonary fibrosis is complex and involves interrelated signalling pathways, the critical pathways in that pathogenesis would vary depending upon the presence or absence of macrophages and their interactions with fibroblasts. Here's an overview of [31].

8.1. TGF-β/Smad Signaling Pathway

Transforming Growth Factor-beta (TGF-β) is a central mediator of fibrosis, essential for fibroblast activation and the production of extracellular matrix proteins. When bound to cell surface TGF-β receptors and phosphorylated by the receptor, the Smad family of proteins becomes activated. Upon activation, the Smad proteins translocate to the nucleus, regulate gene expression, and promote fibroblast differentiation to the critical pathways of myofibroblasts, collagen, and other matrix protein products [32].

8.2. NF-κB Signaling Pathway

Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a transcription factor that controls the genes that form the immune or inflammation response. In pulmonary fibrosis, macrophage and fibroblast activation of NF-κB produces proinflammatory cytokines and chemokines that perpetuate the inflammatory response, tissue damage, and fibrosis. In addition, fibroblast proliferation and survival are also regulated by NF-κB signalling.

8.3. JAK/STAT Signaling Pathway

The Janus kinase/signal transducer and activator of the transcription pathway, or JAK/STAT, is a closely inspected signalling cascade controlling immune responses and inflammation. Activating this pathway can transcribe genes, but these genes enhance cell growth, cell survival, and cell differentiation. The cytokine interleukin

6 (IL-6) can be secreted by pulmonary fibrosis and further amplify the pro-fibrotic phenotype of the macrophage and the fibroblast via the JAK/STAT pathway [33].

Diagrammatic representation of the actual contribution of various signaling pathways in the development of pulmonary fibrosis:

Figure 2, the picture embedded in the Pie chart of saturated and maximal densities shall help approximate how weighty different signalling pathways are for pulmonary fibrosis. Each pie segment represents one of the pathways identified to develop the disease. The most significant portions are attributed to the TGF-β and others, suggesting a broad involvement of these pathways in the aetiology of pulmonary fibrosis. TGF-β is well known for its pro-fibrotic solid actions: it induces fibroblast to myofibroblast transition and enhances the synthesis of ECM proteins. Lastly, there is Wnt signalling, which is involved in the development and tissue homeostasis that plays a part in fibrosis Wnt signalling, and Platelet-Derived Growth Factor (PDGF) signalling, which is linked to cell proliferation and migration [34]. Another critical factor affecting the fibrotic environment is the Interleukin-13 (IL-13) signalling pathway, used in immune response and inflammation. The exact representation also reveals that the Epidermal Growth Factor Receptor (EGFR) signalling, which regulates cell development and communication, is also part of the disease process but less prominently compared to the previously discussed pathways. Because pulmonary fibrosis is such a complex and multifactorial disease, the "Others" category is broad and includes several additional pathways, all of which contribute to the development of the disease. Readers will appreciate this pie chart as a simple representation of the complicated relations between signalling pathways in pulmonary fibrosis. This brings the need to reverse the understanding of these pathways to build a model of moving forward that will enable coming up with therapeutic strategies that can address more than one area of the disease.

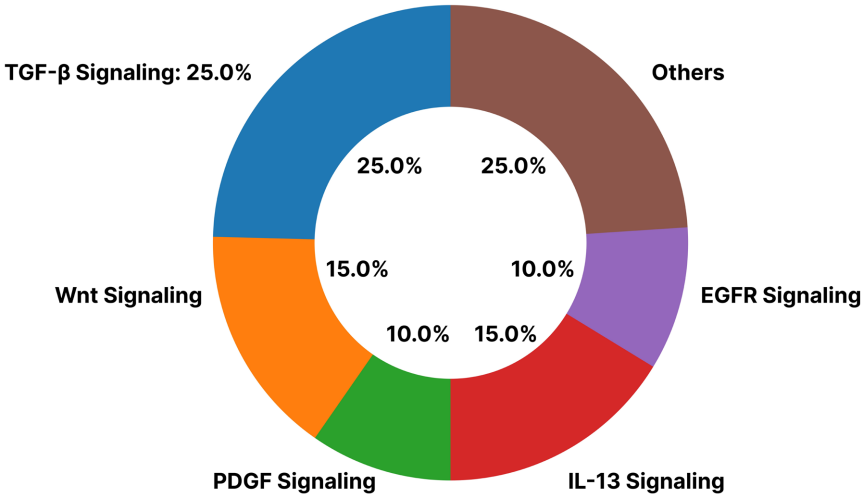

Figure 2. Actual contribution of various signalling pathways in developing pulmonary fibrosis.

9. Other Pathways

9.1. MAPK (Mitogen-Activated Protein Kinase) Pathway

This pathway contains several subfamilies of MAP kinase-like ERK, JNK, and p38 MAP kinase related to cell growth, differentiation, and cell death. Amazingly, dysregulation of the MAPK pathway can result in fantastic amounts of pro-inflammatory cytokines and growth factors, which rev up the whole fibrotic process.

9.2. PI3K/Akt Pathway

The phosphoinositide 3-kinase (PI3K)/Akt pathway is a central signal transduction pathway governing the critical collective functions of cell survival and growth. They reveal that several growth factors and cytokines activate it, possess pro-survival and anti-apoptosis abilities, and enhance cell proliferation and differentiation. In pulmonary fibrosis, it can support the viability of fibroblasts and myofibroblasts and maintain the fibrotic process.

10. Therapeutic Implications

It is encouraging to contemplate the therapeutic strategies that might result from a clearer understanding of macrophages' involvement in pulmonary fibrosis. Here's a closer look at these implications.

Targeting Macrophage Polarization as a Therapeutic Strategy

Modulation of the M1 and M2 phenotype balance is potentially a therapeutic target in the modulation of macrophage polarisation, which is essential in the process of pulmonary fibrosis. Promoting the M1 phenotype should promote pathogen and cellular debris clearance, while inducing the M2 phenotype would be beneficial for tissue repair and inflammation resolution. Yet, the issue is to strike sustained polarization, not to worsen the fibrotic process [35].

Therapeutic implications: Noncoding RNAs, miRNAs, and lncRNAs have become crucial gene regulators in macrophages and other cells subserving pulmonary fibrosis. Expression of specific noncoding RNAs could modulate the course of the disease. Inhibiting miRNAs that promote M1 polarization and fibroblast activation and promoting miRNAs that drive M2 polarisation and anti-inflammatory responses could be beneficial. Likewise, lncRNAs promoting a profibrotic environment may provide new therapeutic avenues.

11. Challenges and Future Directions in Treating Pulmonary Fibrosis

Challenges in Treating Pulmonary Fibrosis

The complexity of pulmonary fibrosis, a disease characterised by slowly progressive scarring of lung tissue, and a still poorly understood cause presents a multifaceted challenge to treating [36]. There are no treatments for this condition other than slowing its progress, often with substantial side effects. Moreover, the disease

has a highly variable progression rate and, until recently, no reliable biomarkers for early diagnosis and monitoring. Current treatment focuses on treating novel pathways with antifibrotic agents, personalised medicine, and cellular and gene therapies (potentially) in future directions. In addition, early detection and lifestyle interventions are increasingly emphasised, and new drugs and strategies exist on the clinical trial front to test the innovative ones. These emerging areas of research and treatment innovation. It holds the hope for improved patient outcomes [37].

Progressed in the treatment of pulmonary fibrosis in the last five years:

Figure 3, the figure shows where we've progressed in treating pulmonary fibrosis in the last five years. The height of each bar indicates the number of significant developments that year, with the bar corresponding to a year from 2019 to 2023. A graph suggests a steady increase in progress, as the number of advancements is increasing yearly, and thus, a significant effort in this field. We approve new drugs, expand clinical trials, discover new biomarkers, advance personalised medicine, and pursue gene therapy. These are important for diagnosing, understanding, and treating pulmonary fibrosis, a chronic, progressive disease that stiffens and scars the lungs. This figure shows how the next step overshadows the previous step, and continuing without a step backwards indicates progress in fighting pulmonary fibrosis. What a confronting reminder that these medical and scientific communities have had to work hard to get treatments for people with this challenging condition.

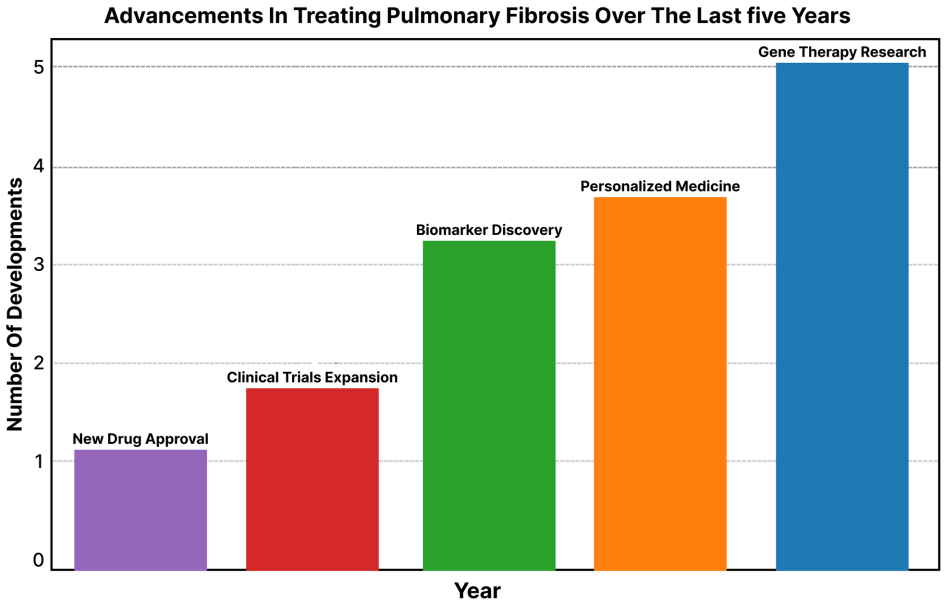

Figure 3. Progress in the treatment of pulmonary fibrosis in the last five years.

12. Future Directions in Treating Pulmonary Fibrosis

A deepened understanding of the mechanisms of pulmonary fibrosis and the adoption of personalised medicine herald the future of pulmonary fibrosis treatment

[38]. To date, researchers are trying to identify new therapeutic targets that better inhibit or reverse the process of fibrosis with a primary focus on antifibrotic agents and anti-inflammatory methods. Another promise comes from developing combination therapeutics (combining existing, already-approved drugs with innovative ones). Regenerative approaches to repair damaged lung tissue are possible if cellular and gene therapies are optimized [39] [40]. Furthermore, the field is fast approaching early detection and intervention strategies, and a critical effort is being made to find sensitive biomarkers and diagnostic tools. The novel treatments are being tested in clinical trials, and the use of lifestyle interventions to work alongside some of the medical therapies that are being explored. Together, these efforts seek to develop more effective, targeted, and patient-specific pulmonary fibrosis treatment to improve the prognosis and quality of life for people with this challenging disease [41]. Pulmonary fibrosis (PF) is a lung disease characterized by progressive scarring of the lung that severely limits the function of the lungs and greatly reduces quality of life. Unfortunately, there are no new forms of treatment for the disease that treat it systematically and no current definitive cure. However, many promising future directions are emerging which may fundamentally change the treatment landscape of PF. Diagnosis, expanded understanding of disease mechanisms, applications of personalized medicine, creation of novel therapeutics, and elaboration of cellular and gene therapies are all included in the case of these diseases.

The first is simply to understand, without a doubt, how the hell PF ever works, to begin with. Over the past few years, studies have shown that the fibrotic process is a complicated, interdependent mix of cell type cell type interactions between macrophages, epithelial cells, fibroblasts and other cell types. In particular, macrophages are phenotypically plastic and can switch between M1 proinflammatory and M2 anti-inflammatory states, both highly implicated in inflammation and tissue repair. Perhaps a novel therapeutic target for pathogen clearance can be the polarization of macrophages to the M1 phenotype, promoting clearance and M2 phenotype, stimulating tissue repair and inflammation resolution. However, the balance of keeping it chronic and balanced but not aggravating fibrosis is yet to be mastered.

Secondly, therapeutic agents are emerging at this time. Currently, available drugs pirfenidone and nonreading have been proven to slow the disease progression, though their effect in reversing fibrosis is quite modest. New targets include the blocking of TGF-β, IL-13, and periotics to reduce fibrotic cytokines. For instance, faralimomab, an anti-TGF-β monoclonal antibody, has been only studied initially, and the results suggest lower levels of collagen and improved lung function. Moreover, the two classes of non-coding RNAs are miRNA and lncRNA, which have been recently identified as important approaches to understanding macrophage regulation and the process of fibrosis. Targeting the miRNAs involved in M1 polarization and fibroblast activation, preferably increasing the levels of the M2-promoting miRNAs, may have therapeutic potential.

Another attractive opportunity is the concept of personalized medicine. Due to the heterogeneity of the disease, these treatments need to be specifically targeted, and through genomic and proteomic profiling, more biomarkers are being discovered that can be used to identify upstream signalling of disease progression and treatment prognosis. For instance, using molecular diagnostics, one can discover patients with TERT, SFTPC, or SFTPA2 gene mutations to whom therapy will be effective. Moreover, the incorporation of artificial intelligence and machine learning concepts in clinical practice can assist in developing screening tools and risk assessments for patients to make appropriate intervention strategies. Significant promise lies in the repair of damaged lung tissue using regenerative medicine (cellular and gene therapies). A potential has been shown in preclinical studies of MSCs because of their immunomodulatory and regenerative properties. MSC therapy is being tested in human patients through clinical trials to measure its safety and overall effectivity, which has been shown early for patients with CF to result in improvements in lung function and quality of life. Taking this further, patient-specific lung cells can be generated using induced pluripotent stem cells (iPSCs) for transplantation and represent an exciting frontier in personalized regenerative medicine.

Finally, the future of PF treatment is in a multi-faceted approach involving the development of novel therapeutic agents, personalized medicine, management regimens, and early detection. Further work and collaboration across disciplines will be needed to translate these exciting directions into practical benefits for patients and thereby improve the prognosis and quality of life in those faced with this difficult disease.

13. Conclusion

In this review, macrophages play a multifaceted part in lung fibrosis, emphasizing M1/M2 phenotypes and their interactions with other cells and pathways. The two macrophage states comprise a delicate equilibrium for immune modulation and pulmonary well-being. The review also reveals the effects of cytokines and non-coding RNAs on the behaviours of macrophages and the fibrotic process. Knowledge of these pathways is the first step to creating drugs or a regimen that can minimise or halt the process of pulmonary fibrosis. These directions include developing molecularly targeted therapies based on the genotype and phenotype of the patients, enhancing diagnostic methods, developing combination therapies, and revealing the potential of ncRNA-based therapy for this multifactorial disease.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Cilli, A. and Uzer, F. (2023) Disease Progression in Idiopathic Pulmonary Fibrosis under Anti-Fibrotic Treatment. *Sarcoidosis, Vasculitis and Diffuse Lung Diseases*, **40**, e2023034.

[2] Wilson, M.S. and Wynn, T.A. (2009) Pulmonary Fibrosis: Pathogenesis, Etiology and Regulation. *Mucosal Immunology*, **2**, 103-121. https://doi.org/10.1038/mi.2008.85

[3] Ghonim, M.A., Boyd, D.F., Flerlage, T. and Thomas, P.G. (2023) Pulmonary Inflammation and Fibroblast Immunoregulation: From Bench to Bedside. *Journal of Clinical Investigation*, **133**, e170499. https://doi.org/10.1172/jci170499

[4] Ma, H., Liu, S., Li, S. and Xia, Y. (2022) Targeting Growth Factor and Cytokine Pathways to Treat Idiopathic Pulmonary Fibrosis. *Frontiers in Pharmacology*, **13**, Article ID: 918771. https://doi.org/10.3389/fphar.2022.918771

[5] Lazar, M., Sandulescu, M., Barbu, E.C., Chitu-Tisu, C.E., Andreescu, D.I., Anton, A.N., *et al.* (2024) The Role of Cytokines and Molecular Pathways in Lung Fibrosis Following SARS-CoV-2 Infection: A Physiopathologic (Re)view. *Biomedicines*, **12**, Article No. 639. https://doi.org/10.3390/biomedicines12030639

[6] Noble, P.W. (2008) Epithelial Fibroblast Triggering and Interactions in Pulmonary Fibrosis. *European Respiratory Review*, **17**, 123-129. https://doi.org/10.1183/09059180.00010904

[7] Sakai, N. and Tager, A.M. (2013) Fibrosis of Two: Epithelial Cell-Fibroblast Interactions in Pulmonary Fibrosis. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1832**, 911-921. https://doi.org/10.1016/j.bbadis.2013.03.001

[8] Zheng, Q., Cox, I.A., Campbell, J.A., Xia, Q., Otahal, P., de Graaff, B., *et al.* (2022) Mortality and Survival in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. *ERJ Open Research*, **8**, Article ID: 00591-2021. https://doi.org/10.1183/23120541.00591-2021

[9] Watanabe, S., Alexander, M., Misharin, A.V. and Budinger, G.R.S. (2019) The Role of Macrophages in the Resolution of Inflammation. *Journal of Clinical Investigation*, **129**, 2619-2628. https://doi.org/10.1172/jci124615

[10] Macrophage Polarization—An Overview. https://www.sciencedirect.com/topics/medicine-and-dentistry/macrophage-polarization

[11] Yunna, C., Mengru, H., Lei, W. and Weidong, C. (2020) Macrophage M1/M2 polarization. *European Journal of Pharmacology*, **877**, Article ID: 173090. https://doi.org/10.1016/j.ejphar.2020.173090

[12] Orecchioni, M., Ghosheh, Y., Pramod, A.B. and Ley, K. (2019) Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS–) vs. Alternatively Activated Macrophages. *Frontiers in Immunology*, **10**, Article No. 1084. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2019.01084/full

[13] Taki, N., Tatro, J.M., Lowe, R., Goldberg, V.M. and Greenfield, E.M. (2007) Comparison of the Roles of IL-1, IL-6, and TNFα in Cell Culture and Murine Models of Aseptic Loosening. *Bone*, **40**, 1276-1283. https://doi.org/10.1016/j.bone.2006.12.053

[14] Chen, S.Z., *et al.* (2023) Macrophages in Immunoregulation and Therapeutics. *Signal Transduction and Targeted Therapy*, **8**, Article No. 207. https://www.nature.com/articles/s41392-023-01452-1

[15] Lee, K.Y. (2019) M1 and M2 Polarization of Macrophages: A Mini-Review. *Medical Biological Science and Engineering*, **2**, 1-5. https://doi.org/10.30579/mbse.2019.2.1.1

[16] Fujiwara, N. and Kobayashi, K. (2005) Macrophages in Inflammation. *Current Drug Target-Inflammation & Allergy*, **4**, 281-286. https://doi.org/10.2174/1568010054022024

[17] Cooke, J.P. (2019) Inflammation and Its Role in Regeneration and Repair: A Caution for Novel Anti-Inflammatory Therapies. *Circulation Research*, **124**, 1166-1168. https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.118.314669

[18] Liu, J., Geng, X., Hou, J. and Wu, G. (2021) New Insights into M1/M2 Macrophages: Key Modulators in Cancer Progression. *Cancer Cell International*, **21**, Article No. 389. https://doi.org/10.1186/s12935-021-02089-2

[19] Peng, H., Xian, D., Liu, J., Pan, S., Tang, R. and Zhong, J. (2020) Regulating the Polarization of Macrophages: A Promising Approach to Vascular Dermatosis. *Journal of Immunology Research*, **2020**, Article ID: 8148272. https://doi.org/10.1155/2020/8148272

[20] Kiecolt-Glaser, J.K., Gouin, J. and Hantsoo, L. (2010) Close Relationships, Inflammation, and Health. *Neuroscience & Biobehavioral Reviews*, **35**, 33-38. https://doi.org/10.1016/j.neubiorev.2009.09.003

[21] Elmore, S. (2007) Apoptosis: A Review of Programmed Cell Death. *Toxicologic Pathology*, **35**, 495-516. https://doi.org/10.1080/01926230701320337

[22] Zhang, J. and An, J. (2007) Cytokines, Inflammation, and Pain. *International Anesthesiology Clinics*, **45**, 27-37. https://doi.org/10.1097/aia.0b013e318034194e

[23] Allen, J.T. and Spiteri, M.A. (2001) Growth Factors in Idiopathic Pulmonary Fibrosis: Relative Roles. *Respiratory Research*, **3**, Article No. 13. https://doi.org/10.1186/rr162

[24] Geiß, C., Salas, E., Guevara-Coto, J., Régnier-Vigouroux, A. and Mora-Rodríguez, R.A. (2022) Multistability in Macrophage Activation Pathways and Metabolic Implications. *Cells*, **11**, Article No. 404. https://doi.org/10.3390/cells11030404

[25] Bissonnette, E.Y., Lauzon-Joset, J., Debley, J.S. and Ziegler, S.F. (2020) Cross-Talk between Alveolar Macrophages and Lung Epithelial Cells Is Essential to Maintain Lung Homeostasis. *Frontiers in Immunology*, **11**, Article ID: 583042. https://doi.org/10.3389/fimmu.2020.583042

[26] Clements, D. and Idoyaga, J. (2021) Alveolar Macrophages and Epithelial Cells: The Art of Living Together. *Journal of Experimental Medicine*, **218**, e20211583. https://rupress.org/jem/article/218/10/e20211583/212622/Alveolar-macrophages-and-epithelial-cells-The-art

[27] Zhou, B.-W., *et al.* (2024) The Role of Macrophage Polarization and Cellular Crosstalk in the Pulmonary Fibrotic Microenvironment: A Review. *Cell Communication and Signaling*, **22**, Article No. 172. https://biosignaling.biomedcentral.com/articles/10.1186/s12964-024-01557-2

[28] Fritsch, S.D., Sukhbaatar, N., Gonzales, K., Sahu, A., Tran, L., Vogel, A., *et al.* (2023) Metabolic Support by Macrophages Sustains Colonic Epithelial Homeostasis. *Cell Metabolism*, **35**, 1931-1943.e8. https://doi.org/10.1016/j.cmet.2023.09.010

[29] Jiang, W., Xu, C., Du, C., Dong, J., Xu, S., Hu, B., *et al.* (2022) Tubular Epithelial Cell-To-Macrophage Communication Forms a Negative Feedback Loop via Extracellular Vesicle Transfer to Promote Renal Inflammation and Apoptosis in Diabetic

Nephropathy. *Theranostics*, **12**, 324-339. https://doi.org/10.7150/thno.63735

[30] Kendall, R.T. and Feghali-Bostwick, C.A. (2014) Fibroblasts in Fibrosis: Novel Roles and Mediators. *Frontiers in Pharmacology*, **5**, Article No. 123. https://doi.org/10.3389/fphar.2014.00123

[31] Hosseinzadeh, A., Javad-Moosavi, S.A., Reiter, R.J., Hemati, K., Ghaznavi, H. and Mehrzadi, S. (2018) Idiopathic Pulmonary Fibrosis (IPF) Signaling Pathways and Protective Roles of Melatonin. *Life Sciences*, **201**, 17-29. https://doi.org/10.1016/j.lfs.2018.03.032

[32] Hata, A. and Chen, Y. (2016) TGF-β Signaling from Receptors to Smads. *Cold Spring Harbor Perspectives in Biology*, **8**, a022061. https://doi.org/10.1101/cshperspect.a022061

[33] Hu, X.Y., *et al.* (2021) The JAK/STAT Signaling Pathway: From Bench to Clinic. *Signal Transduction and Targeted Therapy*, **6**, Article No. 402. https://www.nature.com/articles/s41392-021-00791-1

[34] Liu, J., Xiao, Q., Xiao, J., Niu, C., Li, Y., Zhang, X., *et al.* (2022) Wnt/β-Catenin Signalling: Function, Biological Mechanisms, and Therapeutic Opportunities. *Signal Transduction and Targeted Therapy*, **7**, 1-23. https://doi.org/10.1038/s41392-021-00762-6

[35] Fraser, E. and Hoyles, R.K. (2016) Therapeutic Advances in Idiopathic Pulmonary Fibrosis. *Clinical Medicine*, **16**, 42-51. https://doi.org/10.7861/clinmedicine.16-1-42

[36] White, E.S., Thomas, M., Stowasser, S. and Tetzlaff, K. (2022) Challenges for Clinical Drug Development in Pulmonary Fibrosis. *Frontiers in Pharmacology*, **13**, Article ID: 823085. https://doi.org/10.3389/fphar.2022.823085

[37] Richeldi, L. (2013) Idiopathic Pulmonary Fibrosis: Current Challenges and Future Perspectives. *European Respiratory Review*, **22**, 103-105. https://doi.org/10.1183/09059180.00001413

[38] Libra, A., Sciacca, E., Muscato, G., Sambataro, G., Spicuzza, L. and Vancheri, C. (2024) Highlights on Future Treatments of IPF: Clues and Pitfalls. *International Journal of Molecular Sciences*, **25**, Article No. 8392. https://doi.org/10.3390/ijms25158392

[39] Bonella, F., Spagnolo, P. and Ryerson, C. (2023) Current and Future Treatment Landscape for Idiopathic Pulmonary Fibrosis. *Drugs*, **83**, 1581-1593. https://doi.org/10.1007/s40265-023-01950-0

[40] White, E.S., *et al.* (2016) An American Thoracic Society Official Research Statement: Future Directions in Lung Fibrosis Research. *American Journal of Respiratory and Critical Care Medicine*, **193**, 792-800. https://www.atsjournals.org/doi/10.1164/rccm.201602-0254ST

[41] Bouros, D. and Antoniou, K.M. (2005) Current and Future Therapeutic Approaches in Idiopathic Pulmonary Fibrosis. *European Respiratory Journal*, **26**, 693-703. https://doi.org/10.1183/09031936.05.00145004