Review

CTHRC1: An Emerging Biomarker in Lung Fibrosis

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Review

CTHRC1: An Emerging Biomarker in Lung Fibrosis

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Abstract Pulmonary fibrosis is a chronic, progressive, and irreversible lung disease characterized by fibrotic scarring in the lung parenchyma. This condition involves the excessive accumulation of extracellular matrix (EM) due to a persistently activated wound-repair response. The aberrant activation of myofibroblasts in the alveolar environment by Transforming Growth Factor beta (TGF-β) and other signaling molecules is considered a key event in the development and progression of fibrosis. A primary target of TGF-β signaling in fibrosis is Collagen Triple Helix Repeat Containing 1 (CTHRC1), a secreted glycoprotein that plays a pivotal role in extracellular matrix deposition. CTHRC1 is transcriptionally regulated by TGF-β and inhibits both TGF-β and canonical Wnt signaling pathways. This dual function suggests that CTHRC1 is vital in regulating tissue remodeling during wound repair. In this review, we will highlight recent studies suggesting that CTHRC1 can serve as a diagnostic and prognostic biomarker for fibrosis in idiopathic pulmonary fibrosis, rheumatoid arthritis-interstitial lung disease, systemic sclerosis, and post-COVID lung fibrosis. Notably, the expression of CTHRC1 is responsive to antifibrotic drugs such as pirfenidone indicating its potential as a therapeutic target. Collectively, these findings suggest that CTHRC1 may present new opportunities for the diagnosis, stratification, and treatment of patients with lung fibrosis.

Keywords: biomarker; CTHRC1; extracellular matrix; interstitial lung disease; idiopathic pulmonary fibrosis; rheumatoid arthritis; post-COVID; pirfenidone

1. Introduction

Diffuse parenchymal lung diseases (DPLDs) encompass a diverse array of disorders (Figure 1), primarily characterized by progressive fibrosis of the pulmonary architecture, frequently culminating in respiratory failure [1,2]. Despite the varied etiologies of these pulmonary disorders, the majority exhibit aberrant fibrotic proliferation and infiltration of inflammatory cells as principal clinical manifestations, impacting the alveolar walls of the lungs. These pathological aberrations are predominantly observed in the lung interstitium, hence the alternate designation of interstitial lung diseases (ILDs) [3].

Idiopathic pulmonary fibrosis (IPF) is the most prevalent fibrotic ILD, characterized by the radiographic and histopathological pattern of usual interstitial pneumonia (UIP) in the absence of an identifiable etiology or association with a known cause of pulmonary fibrosis [4]. IPF is chronic and irreversible and frequently results in respiratory failure and mortality. IPF exhibits a higher incidence in males than females and is more prominent among individuals aged 60 years and above [5]. In contrast, other ILDs typically present at a younger mean age (20 to 60 years) and display an equal distribution between the sexes [5,6].

For classification and therapeutic considerations, ILDs are usually assigned to distinct disease categories (Figure 1), primarily based on the presence of an underlying medical condition (e.g., pulmonary fibrosis associated with rheumatoid arthritis), an inciting factor (e.g., pneumoconiosis), or the absence of an identifiable etiology (e.g., IPF) [7–10].

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Symptoms of ILDs often overlap with those of other respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, or even heart failure. This makes it difficult to diagnose and stratify patients based solely on clinical presentation. Advances in molecular diagnostics and identification of disease biomarkers may provide a more accurate diagnosis and classification and may lead to additional treatment options [11]. In addition, biomarkers may improve the monitoring of treatment and outcomes. Recent research has highlighted the role of CTHRC1, a secreted protein involved in extracellular matrix (ECM) and tissue remodeling, as a biomarker for lung fibrosis and, together with co-expressed proteins, as a marker for disease diagnosis and the monitoring of pirfenidone treatment [12–15].

This review will focus on the pathophysiological characteristics of pulmonary fibrosis and its association with rheumatoid arthritis, as well as the potential role of CTHRC1 as a biomarker for both diseases.

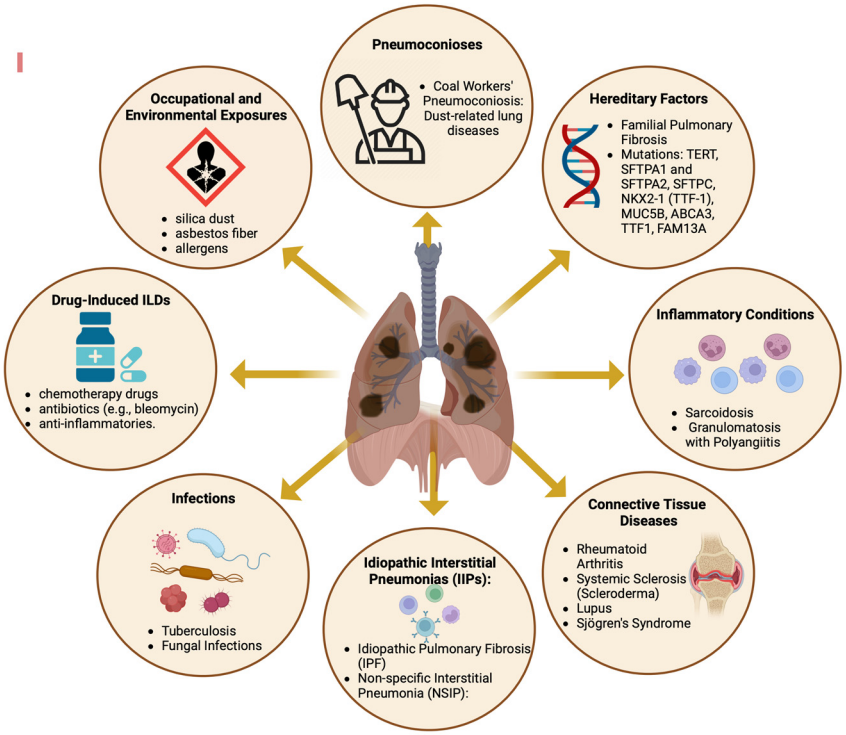

Figure 1. The causes and contributing factors of diffuse parenchymal lung diseases (DPLDs). Created with BioRender.com.

2. Epidemiology

Despite the relatively low incidence of specific fibrosing ILDs, these conditions collectively impact a significant number of patients. Current estimates indicate 76.0 ILD cases per 100,000 individuals in Europe and 74.3 cases per 100,000 in the United States [16]. The most prevalent fibrotic ILDs include sarcoidosis, connective tissue disease (CTD)-associated ILDs, and IPF, with prevalence estimates of 30.2, 12.1, and 8.2 cases per 100,000 individuals [2,16].

Recent investigations have revealed that lung fibrosis affects approximately 70% of patients with rheumatoid arthritis (RA). This observation suggests that extra-articular manifestations of RA contribute to adverse patient outcomes in an estimated 5-10% of established RA patients [17–19].

3. Pathogenesis of lung fibrosis

The precise pathogenesis of fibrosing ILDs remains incompletely understood. In the context of pulmonary fibrosis, diverse disease-specific triggers initiate abnormal cascades of inflammatory responses, culminating in the synthesis, deposition, contraction, and remodeling of ECM components

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and the formation of fibrotic tissue (Figure 2). Numerous aspects of the etiology of specific diseases and the criteria demarcating normal wound healing from fibrotic progression remain obscure. Notwithstanding the myriad etiologies underlying pulmonary fibrosis, the advanced stages exhibit shared pathophysiological mechanisms [20,21].

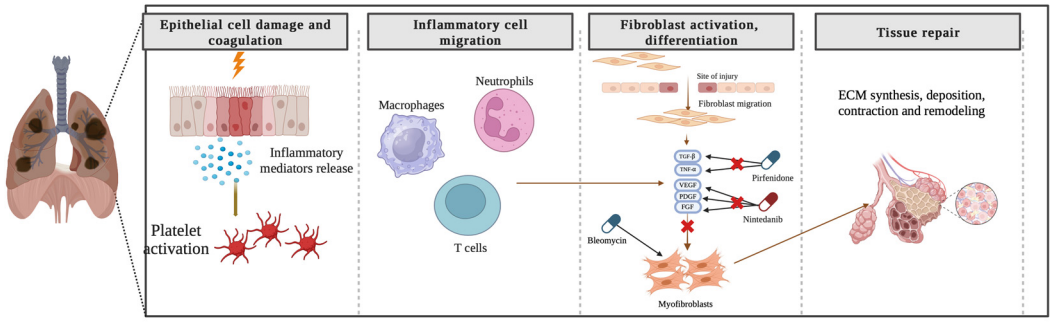

Figure 2. Pathogenesis of Pulmonary Fibrosis: Unraveling the Cascade of Inflammatory Responses and Fibrotic Remodeling. Created with BioRender.com.

Genetic studies have identified both common and rare susceptibility loci associated with pulmonary fibrosis [22]. For instance, a common polymorphism in the *MUC5B* promoter, which is implicated in airway clearance and microbial host defense, has been correlated with an increased risk of IPF, rheumatoid arthritis with ILD (RA-ILD) [23], and chronic hypersensitivity pneumonitis (CHP) [24] but not with systemic sclerosis-ILD (SSc-ILD), sarcoidosis, or antisynthetase syndrome. Patients with IPF, RA-ILD, and CHP exhibit telomere shortening and alterations in the telomere-related genes *TERT*, *TERC*, *RTEL1*, and *PARN* [23,24]. Certain rare genetic variations, including genetic mutations affecting telomeres, are strongly associated with progressive disease [23].

In addition to shared genetic risk factors, the early stages of various ILDs exhibit heterogeneous and overlapping molecular pathways [7]. In IPF, an unidentified disruption of alveolar epithelial cell integrity might trigger pathology through interactions between endothelial cells and myofibroblasts [6]. In sarcoidosis, only a small fraction of patients develops fibrosis in response to granulomatous inflammation caused by a putative, persistent, and yet-to-be-identified etiology [25].

In a substantial proportion of SSc-ILD patients, an amalgamation of inflammatory responses, endothelial dysfunction, and vasculopathy contributes to pulmonary fibrosis, ultimately determining the disease outcome [20]. Investigation into specific cases has indicated that varied inflammatory responses may foster a profibrotic environment and cytokine milieu characterized by transforming growth factor, connective tissue growth factor, platelet-derived growth factor, and the activation of Wnt and Hedgehog signaling pathways. The complex interplay of signaling processes may initiate and sustain fibroblast activation and differentiation into myofibroblasts, leading to fibrosis development, including pathologic collagen deposition and scar formation [20].

4. CTHRC1—structural characteristics and expression

CTHRC1 is a secreted, highly conserved ECM glycoprotein that is pivotal in orchestrating vascular remodeling and tissue repair processes while promoting cell migration [26,27]. CTHRC1 encompasses an NH2-terminal peptide, a short collagen triple helix repeat comprising 36 amino acids, and a COOH-terminal globular domain [26]. Secreted CTHRC1 (30 kDa) observed in higher-order complexes exhibits a considerably increased molecular weight in comparison to cellular CTHRC1 (26 kDa) [28].

CTHRC1 is transiently expressed during adventitial remodeling and primarily associates with myofibroblasts. Under normal conditions, CTHRC1 is undetectable in healthy arteries and is predominantly expressed in various mesenchymal-derived cells during growth and injury-induced tissue repair [27,28]. During skeletal development, abundant CTHRC1 expression is observed in cartilage primordia, growth plate cartilage, bone matrix, and periosteum. In other tissues, CTHRC1

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expression overlaps considerably with interstitial collagens and transforming growth factor-β (TGF-β) family members, indicating substantial collagen synthesis in the presence of TGF-β. Furthermore, the activation of TGF-β signaling may promote the proliferation and migration of vascular smooth muscle cells, resulting in neointimal hyperplasia [29,30]. Pathological expression of CTHRC1 has also been detected in the matrix of calcifying atherosclerotic plaques and mineralized bone tissues [31].

Elevated CTHRC1 expression has been implicated in the pathophysiology of numerous cancerous and autoimmune disorders. Accordingly, CTHRC1 was identified as a novel oncogene aberrantly overexpressed in various malignant tumors, exhibiting associations with bone metastasis and unfavorable patient outcomes [32–35]. CTHRC1 gene expression is also upregulated in RA, lupus erythematosus, muscular dystrophies, and lung, cardiac, and liver fibrosis [15,36–42]. In contrast, CTHRC1 silencing protects against asthmatic airway remodeling and inflammation both in vitro and in vivo [43].

5. CTHRC1 plays a role in several signaling pathways

CTHRC1 enhances collagen promoter activity by binding to ligands, potentially playing a role in vascular remodeling through the regulation of collagen matrix deposition and cell migration [44]. CTHRC1 directly or indirectly regulates and affects several signaling pathways, such as TGF-β, Wnt, integrin β/FAK, Src/FAK, MEK/ERK, PI3K/AKT/ERK, HIF-1α, and PKC-δ/ERK. The Cthrc1 transcript is induced by both TGF-β and BMP-4, and its inhibition of TGF-β sensitive reporters, along with the observed reduction in phospho-Smad2/3 levels *in vivo*, collectively support the evidence that these proteins could function as antagonists to preserve equilibrium among extracellular matrix components [44]. In addition, CTHRC1 promotes accelerated wound repair in mice by regulating the TGF-β and Notch pathways [45]. Similarly, CTHRC1 may also contribute to IL-1β-induced apoptosis of chondrocytes by activating the JNK1/2 pathway [46]. CTHRC1-expressing synoviocytes exerted an anti-inflammatory effect in a collagen antibody-induced arthritis model [47]. CTHRC1 can also contribute to fat and glycogen synthesis [27,48]. Moreover, CTHRC1 has been identified as a positive regulator of bone homeostasis that increases bone mass by promoting osteoblastic bone formation.

6. CTHRC1 as a biomarker for RA

CTHRC1 has recently been reported as a potential biomarker for RA diagnosis [36]. Initially, CTHRC1 was linked to RA pathogenesis in mice via a *Cthrc1* gene polymorphism, which affected arthritis progression in mouse models. In mice, the *Cthrc1* gene is located within the proteoglycan-induced arthritis 8 (*Pgia8*) locus on chromosome 15, and this locus controls PGIA severity in a sex-specific manner [49,50]. Within the *Pgia8* locus, *Cthrc1* strongly correlated with arthritis severity corresponding to the levels of the proinflammatory cytokines IL-6 and IL-1β [50].

To assess the impact of CTHRC1 on RA in humans, CTHRC1 levels were analyzed in plasma. The results showed a significant increase in individuals with established RA compared to healthy individuals [36]. This elevation was positively associated with RA disease markers, such as RF, anti-citrullinated protein antibodies (ACPA), and C-reactive protein (CRP) [36]. A similar study independently identified CTHRC1 as a diagnostic marker for RA [51]. Together, the findings in mouse models and the observations in patients indicate that CTHRC1 may be a potential biomarker for RA diagnosis. CTHRC1 serum levels may also be a candidate diagnostic biomarker for inflammatory conditions and fibrosis.

In RA patients, in addition to increased serum levels, immunohistochemistry analysis revealed highly elevated CTHRC1 expression at the invasive edge of the pannus [52]. When closely analyzed, two subtypes of fibroblast-like synoviocytes (FLSs) contributed to high expression in isolated tissues from RA patients. One subtype was characterized by the CD34+ CDH11+ THY1/CD90- phenotype and was proposed to recruit monocytes via IL-6, CXCL12, and CCL2. Another phenotype included the expression of CD34− CDH11+ THY1/CD90+, and this subtype was strongly linked with RA pathology [53]. In addition, both subsets also expressed several other genes related to migration and invasion, including *TWIST1*, *POSTN*, *LOXL2*, *PDGFRB*, and *MMP14* [54,55], and these activities were confirmed *in vitro*. Therefore, CTHRC1 may contribute to synovial destruction by modulating the

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migration and invasion of various FLS populations, resulting in an abnormal immune response in RA.

Many studies have revealed CTHRC1 expression in FLSs in RA, and CTHRC1 can participate in the Wnt or TGF-β signaling pathways. Upregulated expression of these signaling pathways is observed in RA [56], is associated with chronic activation of FLSs and drives a localized immune response. This elevated production is associated with *WNT5A* expression, which is detected in FLSs and identified as the primary driver of cytokine production during inflammation [57,58]. Similarly, circulating WNT5A was associated with lung fibrosis associated with RA [59].

7. Common pathogenic pathways in RA-ILD and pulmonary fibrosis

The precise etiology of RA-associated lung fibrosis is not yet known. A complex interplay between genetic and environmental factors may contribute to disease pathogenesis. Individuals with specific, shared HLA-DRB1 epitopes show enhanced susceptibility [60,61]. Environmental risk factors, such as tobacco smoking, may further enhance immunogenicity in these individuals by triggering smoking-induced citrullination of lung proteins [62–64]. Increased citrullination can be a direct target for ACPAs and T-cell-mediated immunity, resulting in immune factors targeting the lung. However, elevated protein citrullination has also been observed in non-smoking individuals, suggesting the potential involvement of additional environmental factors, including particulate matter, silica, atmospheric pollution, and alterations in the pulmonary microbiome [65,66]. These environmental triggers may induce aberrant gene expression and subsequently activate the immune system, leading to the generation of circulating autoantibodies [67]. This process may, in turn, instigate pro-inflammatory cascades, culminating in persistent pulmonary inflammation [67,68].

Lung inflammation may contribute to early RA-related autoimmunity. Multiple mechanisms have been proposed through which mucosal inflammation progresses to joint inflammation [65]. These include commonly shared autoantigens, epitope spreading to a joint-specific antigen and circulating immune complexes that may be responsible for the onset of articular disease. For example, five shared citrullinated target peptides were identified between the lung and synovial tissue, two of which are citrullinated-vimentin peptides [69,70]. These shared autoantigens may provide a direct link between multifactorial diseases involving the lung and joints.

Among RA-associated autoantibodies, increased levels of ACPA, rheumatoid factor (RF), anti-peptidyl arginine deiminases (anti-PADs), and anti-carbamylated protein antibodies are observed three to five years prior to the appearance of clinically apparent inflammatory arthritis (IA) [71–73]. These circulating autoantibodies point to an extra-articular site as the origin of autoimmunity. The mucosal origin of autoimmunity in pre-RA can be supported by the responses of IgA-related autoimmunity, particularly IgA-ACPA responses [74]. To date, among mucosal sites, the lung has been extensively studied due to the high number of reports of lung diseases preceding joint destruction in RA [75]. In addition, organized lymphoid areas in the lungs, named inducible bronchus-associated lymphatic tissue (iBALT), are implicated in RA-related autoimmunity [76]. Other proposed autoimmunity triggers include mucosal inflammation in the gut and/or gingiva, and more research is needed to fully understand the contribution of these sites to autoimmunity in RA [77–79].

The concept of a shared pathogenic mechanism underlying the development of RA-ILD and IPF is supported by phenotypic similarities and shared environmental risk factors. The discovery of an excess of uncommon genetic variations found in RA-ILD patients linked to familial pulmonary fibrosis provides further support [80]. Notably, there was an excess of variants in genes involved in telomere maintenance (*TERT, PARN, RETL1*) and in the gene *SFTPC,* which encodes a protein involved in surfactant homeostasis, with an odds ratio (OR) of 3.17 when compared to controls [80]. Although these findings point to a shared genetic background between RA-ILD and IPF, at least for rare variants, one of the main limitations was the absence of patients with RA without ILD in the control group. Thus, these findings do not rule out the possibility that these mutations impact the genetic predisposition to RA. In addition, a functional *MUC5B* rs35705950 promoter variation, which is a significant risk factor for IPF (OR 8.3; 95% CI, 5.8-11.9; P4.6 × 10^{-31}) [81], was recently discovered to be a risk factor for RA-ILD but was not connected to RA without ILD. Importantly, intense MUC5B

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staining was observed in the hyperplastic alveolar epithelium in fibrotic regions of lung biopsies from individuals with RA-ILD, comparable to what was observed in IPF [23]. This finding clearly indicates that RA-ILD and IPF have the same genetic architecture [23,81].

8. Role of CTHRC1 in pulmonary fibrosis

The fibrotic environment in the lung might be due to chronic Wnt/β-catenin signaling that induces cellular senescence in lung epithelial cells. This chronic increase in Wnt/β-catenin signaling might contribute to the senescence of alveolar type II cells and cell reprogramming, thus leading to further progenitor cell dysfunction and impaired lung repair [82].

In a murine model of bleomycin-induced lung fibrosis, CTHRC1 attenuated fibrotic tissue formation and preserved lung function [41], suggesting that the regulatory activity of CTHRC1 may inhibit TGF-β [44] and indirectly canonical Wnt signaling [28]. In a Cthrc1 knockout murine model, bleomycin administration resulted in increased immune response and decreased lung function, most likely due to the rapid accumulation of collagen in the lung [41]. These observations underscore the significant role that CTHRC1 plays in modulating lung matrix biology.

Analogous clinical manifestations are observed in patients with lung fibrosis, including breathing problems that result in severe dyspnea in the later stage of the disease. In patients, these signs and symptoms are typically preceded by months of undetected early disease progression [83]. Several studies have consistently reported that the invasive phenotype of fibroblasts drives pulmonary fibrosis in the bleomycin-induced murine model [84,85]. Significantly, CTHRC1 levels were elevated in these pathological fibroblasts. One study identified a fibroblast subset populating the fibrotic lungs of both mice and humans, characterized by high levels of type 1 collagen production, particularly *COL1A1* and *COL3A1,* and increased expression of *CTHRC1* [15]. Importantly, these *COL1A1*+ and *CTHRC1*$^{+}$ cells were designated as 'pathological fibroblasts,' given their enhanced migratory capacity to colonize the lung and their localization at the edge of fibrotic processes [15]. Another study corroborated these results and further showed that inhibition of the CTHRC1/HIF-1α axis by NEDD4L-induced β-catenin ubiquitination impedes the initiation and progression of interstitial lung fibrosis [86].

Similarly, CTHRC1 has emerged as a marker of activated fibroblasts driving the development of SSc. Previous studies implicated the TGF-β-responsive genes periostin (POSTN) and cartilage oligomeric matrix protein (COMP) as biomarkers of activated TGF-β signaling and showed that POSTN and COMP exhibit heightened expression in the skin, manifest correlation with modified Rodnan skin score (mRSS), and demonstrate predictive value concerning disease progression [87,88]. In both dermal tissues from SSc patients and skin tissues from mice with bleomycin-induced fibrosis, *CTHRC1* expression was elevated along with *POSTN* and other pathologic ECM components [89,90]. In the bleomycin-induced murine model of dermal fibrosis, recombinant CTHRC1 inhibited TGF-β-stimulated collagen deposition by fibroblasts and reduced fibrotic changes [91].

Taken together, the elevated expression of CTHRC1 in a subset of pathological fibroblasts driving fibrosis development suggests that it might be a key player in driving fibrotic processes by contributing to abnormal tissue repair, ECM remodeling, and myofibroblast activation. The identification of CTHRC1 as a marker for pathologic fibroblasts highlights its potential as a diagnostic biomarker for fibrotic diseases, including IPF, RA-ILD, and SSc. Targeting CTHRC1 and the signaling pathways it influences could offer novel therapeutic strategies to mitigate fibrosis progression and improve patient outcomes.

9. CTHRC1: A Potential Prognostic Marker for Severe Lung Complications in COVID-19 Patients

The coronavirus disease 2019 (COVID-19) pandemic due to the SARS-CoV-2 virus caused a range of symptoms in affected individuals, from asymptomatic cases to severe conditions that resulted in lung fibrosis and potentially fatal respiratory failure [92]. Lung tissue affected by COVID-19 showed a considerable increase in the number of cells from the monocyte-macrophage lineage [71,93], and these were predominantly located in the extravascular lung tissue, which is primarily 'interstitial' rather than 'alveolar' [71,73]. These macrophage populations were described as

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extremely active and expressed inflammatory markers as well as genes linked with tissue repair and fibrogenesis [14,94].

Patients experiencing long-haul COVID display enduring disruptions in immune responses even 8 months post-infection. This is evident through persistent increases in activated CD14+CD16+ monocytes and plasmacytoid dendritic cells compared to controls. Additionally, sustained elevation in type I (IFNβ) and type III (IFNλ1) interferons persists, which, along with other factors such as pentraxin 3, IFNγ, IFNλ2/3, and IL-6, forms a combination indicative of long-haul COVID, with accuracies reaching 78.5% to 81.6% [95]. These elements, often tied to acute severe disease, imply a delayed or ineffective resolution of inflammation in these patients. Conversely, overly intense inflammatory responses may precipitate irreversible lung fibrosis, causing significant respiratory function impairment. Markers, such as lipocalin-2, matrix metalloprotease-7, and hepatocyte growth factor, closely align with inflammation severity and impaired pulmonary function [96]. The capacity of SARS-CoV-2 to alter immune homeostasis mechanisms impacting tissue inflammation likely underlies persistent lung injuries. The decline in alveolar macrophages, integral for lung integrity, in severe COVID-19 may stem from damage to alveolar type II cells, which also express ACE2 receptors that the virus targets [97–99]. In COVID-19 fatalities, lung analyses have unveiled inflammation-associated AT2 cell states that hinder proper regeneration, coupled with pathogenic fibroblasts expressing CTHRC1, possibly driving rapid pulmonary fibrosis progression [100]. TGF-β and epithelium-derived IL-6 could be implicated in this fibrotic process [14,15,101]. Macrophages have been implicated in the immunopathology observed in fatal COVID-19 cases, and profibrotic macrophages, particularly those involving interleukin 1 beta (IL-1β), can hinder epithelial repair [14,102]. Importantly, a subpopulation of CTHRC1+ pathological fibroblasts was found to be increased in lungs affected by COVID-19 [15,93] and associated with the progression of pulmonary fibrosis in COVID-19 patients [14,100,103]. Researchers identified four fibroblast clusters—adventitial, alveolar, intermediate pathological, and pathological. Remarkably, the latter two cell clusters exhibited substantial expansion in COVID-19 lungs compared to controls and were characterized by the expression of *CTHRC1*, *COL1A1*, and *COL3A1* [14,100,103]. These fibroblasts have previously been identified as pathologic drivers of fibrosis in patients with IPF [15]. These cells produce the highest levels of type 1 collagen and have an enhanced capacity to migrate and colonize the lung [15]. The increased risk of developing fibrosis could be attributed to the emergence of these CTHRC1+ fibroblast populations, as well as their demonstrated close relationship to macrophages [71,93].

A recent study discovered overexpression of profibrotic genes, including collagen and *POSTN*, in COVID-19 patients. This study further confirmed a significant increase in the expression of *CTHRC1*, a marker for myofibroblasts, colocalizing with regions of high alpha-smooth muscle expression [104–106]. Importantly, pulmonary fibrosis can develop and persist even after a patient fully recovers from COVID-19, emphasizing the need for diagnostic biomarkers and long-term treatment options to slow the progression of the disease [107].

Overall, these findings suggest that CTHRC1 may serve as a diagnostic biomarker for patient stratification. Additionally, targeting CTHRC1 expression may represent a potential therapeutic avenue for slowing the progression of fibrosis in patients who experience severe COVID-19 symptoms.

10. Targeting CTHRC1: Therapeutic options for lung fibrosis

Numerous compounds with diverse mechanisms of action are currently being evaluated in clinical trials as potential anti-fibrotic drugs [108]. These drugs target specific pathways and molecules that play critical roles in the development and progression of fibrosis. The drugs are often categorized based on their primary targets, and their efficacy is being assessed across various fibrotic diseases. TGF-β is a central player in fibrosis, and several drug categories are designed to modulate its effects. Pirfenidone, an FDA-approved drug for IPF, inhibits TGF-β synthesis and activation [109]. It has shown effectiveness in reducing lung function decline and mortality in IPF patients [13,110].

Nintedanib, a receptor tyrosine kinase inhibitor, has shown benefits in reducing fibrosis and disease progression in IPF [109]. In a mouse model of RA-ILD, nintedanib was found to inhibit the development of lung fibrosis [111,112]. Nintedanib has been investigated in two randomized, double-

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blind placebo-controlled trials, one of patients with SSc-ILD and one of patients with progressive fibrosing ILD. Both studies showed that nintedanib reduced the decline in forced vital capacity (FVC) [113,114]. ZSP1603, which blocks PDGFRs, FGFRs, and VEGFR2, exhibits anti-fibrotic effects in preclinical models [115]. In addition, Pamrevlumab, an anti-CTGF antibody, has demonstrated efficacy in early-phase trials for IPF [116,117].

The antifibrotic properties of pirfenidone were evaluated in a double-blind, randomized placebo-controlled trial in patients with non-IPF progressive fibrotic ILDs. The study suggested that pirfenidone added to conventional therapy reduced the decline in FVC [118]. This finding may be linked to pirfenidone significantly inhibiting CTHRC1 expression in the bleomycin-induced lung fibrosis model in mice [12]. Since pathological CTHRC1+ fibroblasts were strongly involved in ensuing fibrosis progression in COVID-19 patients, these findings raised the possibility of including pirfenidone within a standard treatment protocol to improve the outcome of post-COVID lung fibrosis patients. Interestingly, recent studies suggest that treating COVID-19 patients with pulmonary fibrosis using pirfenidone, particularly in the early stages of fibrosis, can improve patient outcomes, thus offering a promising therapeutic approach [119–121].

11. Conclusion

The information discussed in this review highlights the potential of CTHRC1 as a biomarker for the early detection of pulmonary fibrosis and as a possible target for the development of novel therapeutic strategies. Recent studies have underscored the importance of CTHRC1 in relation to RA-associated pulmonary fibrosis and its regulatory role in maintaining the integrity of the lung matrix. The potential disruption of CTHRC1-related processes might contribute to the abnormal proliferation of fibroblasts and their transformation into invasive phenotypes. In addition, other research has indicated the potential involvement of CTHRC1 in ECM remodeling in different tissues, including hepatic and cardiac fibrosis. The current understanding of CTHRC1 is consistent with its modulatory effects on fibroblast proliferation mediated by the TGF-β and canonical Wnt signaling pathways, as well as EMT. Additional research is necessary to clarify the more specific downstream actions of CTHRC1, aiming to identify potential strategies for therapeutic targeting to manage the progression of RA-related pulmonary fibrotic disease. Furthermore, CTHRC1 alone or as part of a pro-fibrotic gene expression signature could serve as a marker that could aid in the development of more effective diagnostic tools, preventive measures, or targeted therapeutic interventions for the progression of fibrosis and inflammation in DPLDs. CTHRC1 could offer new avenues for the early stratification of patients allowing more effective targeted treatment options.

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