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Review

Pulmonary fibrosis from molecular mechanisms to therapeutic interventions: lessons from post-COVID-19 patients

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ABSTRACT

Pulmonary fibrosis (PF) is characterised by several grades of chronic inflammation and collagen deposition in the interalveolar space and is a hallmark of interstitial lung diseases (ILDs). Recently, infectious agents have emerged as driving causes for PF development; however, the role of viral/bacterial infections in the initiation and propagation of PF is still debated. In this context, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the current coronavirus disease 2019 (COVID-19) pandemic, has been associated with acute respiratory distress syndrome (ARDS) and PF development. Although the infection by SARS-CoV-2 can be eradicated in most cases, the development of fibrotic lesions cannot be precluded; furthermore, whether these lesions are stable or progressive fibrotic events is still unknown.

Herein, an overview of the main molecular mechanisms driving the fibrotic process together with the currently approved and newly proposed therapeutic solutions was given. Then, the most recent data that emerged from post-COVID-19 patients was discussed, in order to compare PF and COVID-19-dependent PF, highlighting shared and specific mechanisms. A better understanding of PF aetiology is certainly needed, also to develop effective therapeutic strategies and COVID-19 pathology is offering one more chance to do it. Overall, the work reported here could help to define new approaches for therapeutic intervention in the diversity of the ILD spectrum.

1. Introduction to lung fibrosis

The term “pulmonary fibrosis” (PF) defines a pathological state in which the lung parenchyma undergoes an irreversible process of overgrowth, hardening, and/or scarring often attributed to excess deposition of extracellular matrix components including collagen. Interstitial lung diseases (ILDs) are a heterogeneous group characterized by different clinical, radiologic, and pathologic patterns that extensively involve the lung parenchyma. PF is a hallmark of different types of ILDs [1] that share the presence of chronic inflammation and/or collagen deposition in the interalveolar space, leading to a deficient transit of oxygen and carbon dioxide molecules across the alveolar epithelium. Some ILDs are characterized by different degrees of PF, in particular, idiopathic pulmonary fibrosis (IPF) is considered the most representative type of lung fibrosis. IPF has the worst prognosis with a median survival of 2–5 years after diagnosis, a prognosis worse than that of many cancers, and indeed represents a huge unmet medical need [2,3]. IPF manifests in the older age (rarely earlier than 60 years), with a prevalence higher in men than women, and in the absence of any obvious provocation [1]. PF represents also the end-stage of ILD related to well-known connective tissue diseases (e.g. rheumatoid arthritis and systemic sclerosis) but also other less-characterized connective tissue diseases related to exposure to drugs or asbestos [3].

The last 20 years have witnessed the succession of numerous different points of view in the scientific and medical communities of PF in general leading to a progressive transformation of the landscape of this pathology. The first debated point is the identification of the driving cause of PF. PF has been primarily considered an epithelial-driven disease in which dysfunctional alveolar cells take an etiological precedent. Other authors focused on the augmented extracellular deposition of collagen within the interstitium and the activation of the immune system as pathological mechanisms of PF onset. It is now becoming clear that all these events belong to a unique pathophysiological chain of events that accounts for PF progression [4]. Thus, the key question that

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needs now to be addressed is how the onset and progression of PF occur, based also on different genetic, epigenetic, and environmental backgrounds [5].

In this complex and evolving scenario, interesting new details have been added in the last two years due to the protracted battle against the pandemic by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease (COVID-19). SARS-CoV-2 viral infection has been demonstrated to induce acute respiratory distress syndrome (ARDS) in an estimated 17.2 to 31% of COVID-19 infections [6]. PF is a well-known complication of ARDS that is histologically characterized by diffuse alveolar damage (DAD). The first study about post-COVID-19 evaluation demonstrated that while the majority of patients recover without residual lung damage, an appreciable number (more than a third of recovered patients) experience residual fibrotic lesions that are reversible in some cases [7,8]. Given the widespread incidence of the pandemic, this translates into a few million people left with significant pulmonary involvement.

Herein, the main molecular mechanisms driving the onset of PF regardless of their aetiology will be reviewed and discussed, along with an overview of how these studies have been translated into approved or proposed diagnostic/therapeutic solutions. A specular approach will be used to discuss the lung fibrosis cases documented in COVID-19 patients. This will hopefully highlight the shared mechanistic details and help to define better strategies for therapeutic intervention in these two pathological states.

2. Molecular mechanisms of fibrosis: What is known and what is unknown

Several mechanisms have been demonstrated to play a role in the fibrosis insurgence and progression; nevertheless, the pathophysiology of fibrotic processes is still incompletely defined. Several types of cells participate in the initiation and progression of fibrosis such as Alveolar epithelial type I cells (AT1), Alveolar epithelial type II cells (AT2), resident fibroblasts, resident and circulating cells of the immune system (monocytes, macrophages, lymphocytes, and neutrophils) and mesenchymal stem cells (MSCs) [9]. Of particular interest, besides the specific role of each cell type, is the crosstalk among them that crucially determines the amplification and complexity of the fibrotic process.

In the lung, the initiation is followed by an inflammatory process that causes a huge activation of resident immune cells. The activated macrophages and neutrophils release pro-fibrotic mediators that promote the accumulation of myofibroblasts [10]. These are particular types of cells capable to produce extracellular matrix (ECM) and with enhanced contractility [11]. Lung myofibroblasts can originate from different sources and their fate is apoptosis allowing the termination of the healing process [12]. Unfortunately, during the fibrotic process, the termination of ECM production from these cells is impaired and the

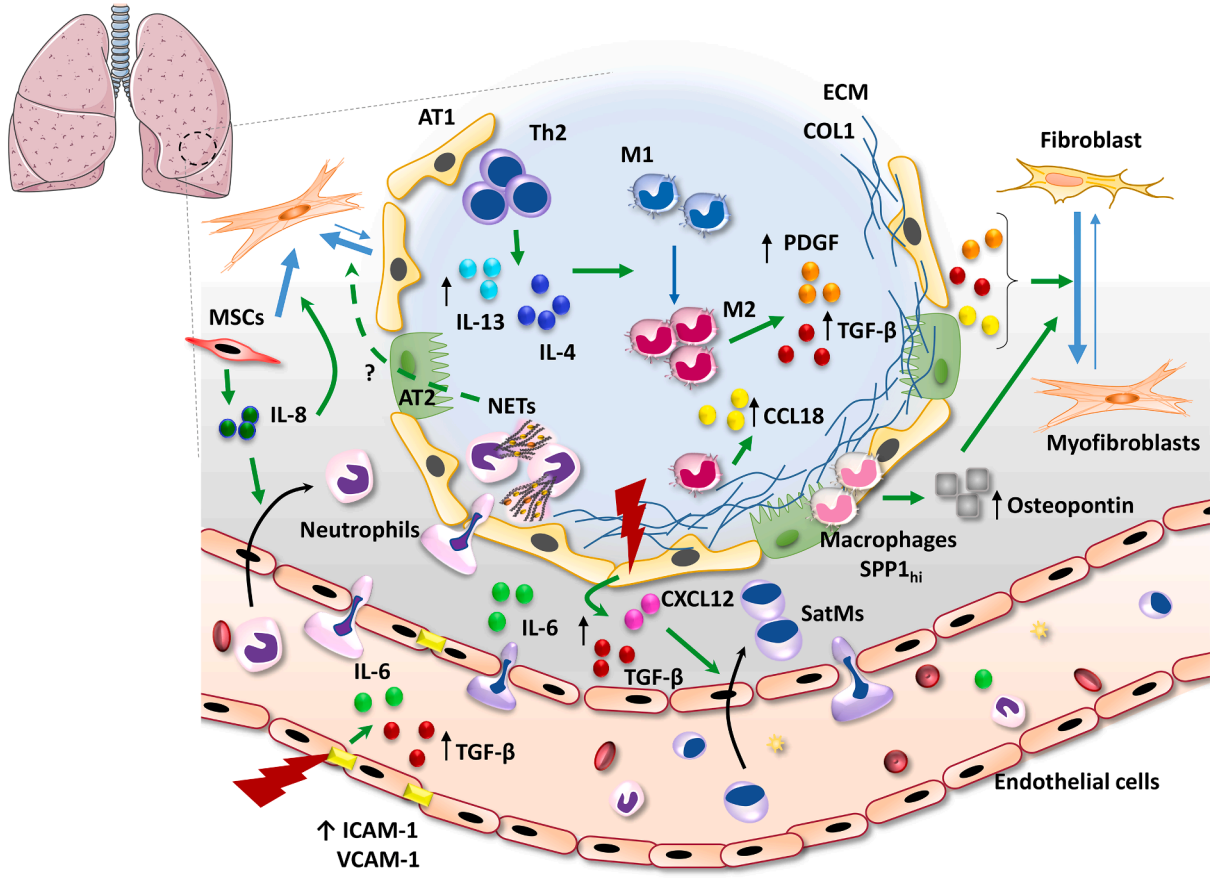

Fig. 1. Schematic representation of the immune system involvement in the induction of pulmonaryl fibrosis (PF). Upon endothelial and epithelial injury, cytokines such as tumor growth factor–β (TGF-β), interleukin-6 (IL-6), C-X-C motif chemokine ligand 12 (CXCL12) are released. These cytokines contribute to the activation and recruitment of immune cells (macrophages, SatMs, and neutrophils). T helper 2 (Th2) cells release IL-13 and IL-4 that promote the polarization of macrophages to M2 phenotype (M1: classically activated macrophages phenotype, pro-inflammatory; M2: alternatively activated macrophages phenotype, anti-inflammatory). The M2 cells produce a large amount of TGF-β and the platelet-derived growth factor (PDGF) further contributing to the fibrotic process. Pro-inflammatory cytokines also cause the neutrophil extracellular traps (NETs) formation that contributes to epithelial damage. Green arrow: activation. Black arrow: migration. Light blue arrow: transformation. ECM: extracellular matrix; COL1: collagen type 1; AT1: alveolar epithelial type I cells; AT2: alveolar epithelial type II cells; MSCs: mesenchymal stromal cells; CCL18: C—C motif chemokine ligand 18; ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1.

increased stiffness causes further cell injury and further myofibroblast activation [13]. When this occurs, the self-amplifying activation loop is established and the fibrotic process becomes irreversible. Herein, the most recent and the main consolidated mechanisms activated during the fibrotic process will be discussed (Figs. 1 and 2).

2.1. Initiation of the fibrotic lung alteration

Injuries in the endothelium and epithelium have arisen as a general mechanism of fibrosis initiation [14]. The lung epithelium can be subjected to different micro-injuries, for example from cigarette smoke and toxins [15]. Recently, it has become more evident that also viral infections such as cytomegalovirus and SARS-CoV-2 can cause significant lung injury leading to both endothelial and epithelial damage acting as starting point for the extensive inflammatory and fibrotic processes [16,17]. However, the exact role of viral, as well as bacterial infection, in the initiation and propagation of PF is still debated.

Regardless of the origin, the endothelial injury (Fig. 1) causes the release of pro-fibrotic factors and cytokines such as transforming growth factor–β (TGF-β), connective tissue growth factor/CCN family member 2 (CTGF/CCN2), and plasminogen activator inhibitor–1 (PAI-1) that sustain all the phases of fibrotic processes [14]. In this scenario, ageing has emerged as a critical player too. Indeed, Caporarello et al. have evidenced that endothelial cells from aged mice have elevated pro-fibrotic and reduced vascular homeostasis regulation. In fact, the injured aged cells fail to upregulate genes such as the nitric oxide synthase 3 (Nos3), encoding the enzyme endothelial nitric oxide synthase (eNOS), which is a pivotal protein involved in the resolution of lung fibrosis [18].

Injured endothelial cells also express increased levels of adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E- and P-selectins [19,20], which facilitate immune cell recruitment. In turn, infiltrating immune cells release pro-inflammatory cytokines, such as interleukin 6 (IL-6) that further enhance the endothelial cell inflammation in a positive feedback loop.

2.2. Immune system activation

2.2.1. Macrophages

Lung macrophages are the first line of defence against pathogens and antigens. Recently, based on their origin, distinct macrophage populations have been identified in the lung: resident macrophages and monocyte-derived macrophages [21]. Tissue-resident alveolar macrophages derive from yolk sac foetal progenitors and maintain self-renewal properties over the lifespan. In response to injury, alveolar macrophages undergo pyroptosis causing their depletion, thus, blood-derived monocytes are recruited to the lung where cytokines drive their differentiation into alveolar macrophages. Macrophages have two distinct polarization states: classically activated phenotype (M1), which is closely linked to pro-inflammatory processes, and the "alternatively activated phenotype" (M2), which is involved in tissue repair and anti-inflammatory reactions (Fig. 1). Of note, to date, this classification is

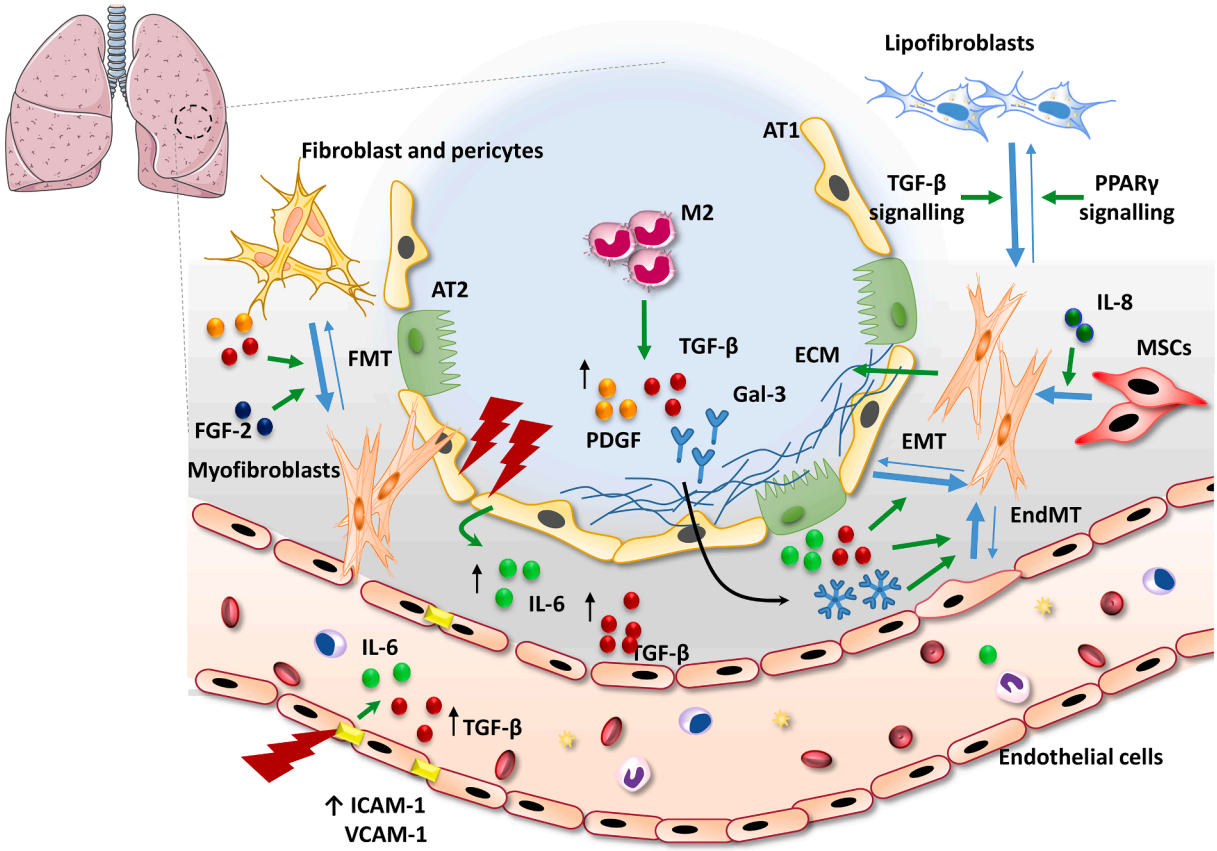

Fig. 2. Schematic representation of the mechanism regulating myofibroblasts activation in pulmonaryl fibrosis (PF). Soluble mediators such as tumor growth factor–β (TGF-β), interleukin-6 (IL-6), and galectin-3 (Gal-3) promote the transformation of endothelial cells to myofibroblasts (EndMT). Similarly, TGF-β, and IL-6 favour the epithelial-mesenchymal transition (EMT) of alveolar endothelial type 1 (AT1) cells. Another source of myofibroblasts derives from the activation of resident fibroblast and pericytes by TGF-β, the platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (FGF-2) in a process defined fibroblast to myofibroblast transformation (FMT). The activation of TGF-β signalling promotes the formation of myofibroblast from lipofibroblasts. Despite the activation of the peroxisome proliferator-activated receptors-gamma (PPARγ) signalling that could counteract the myofibroblast activation, these pathways are downregulated in PF. The release of IL-8 can also drive the activation of mesenchymal stromal cells (MSCs). The increase of myofibroblast cell bulk causes the over-production of extracellular matrix (ECM).

oversimplified considering the complexity of the stimuli in pathological conditions [22]. Surprisingly, the M2 phenotype, but not the M1, plays a major role in the progression of lung fibrosis [23]. Initially, after the lung injury, resident macrophages are polarized to the M1 phenotype due to the presence of interferon-gamma (IFN-γ) and toll-like receptor (TLR) ligands. The M1 cells contribute to the host defence against pathogens by generating reactive oxygen species (ROS) and reactive nitric oxide (NO) via inducible nitric oxide synthase (iNOS) and by releasing pro-inflammatory cytokines and chemokines (e.g. IL-1β, IL-12, IL-23, TNF-α, and C—C motif chemokine ligand 2 (CCL2)). In the later phase, the M1 macrophages are replaced by a population of M2 macrophages derived both by the polarization of the resident macrophages and the differentiation of blood-derived monocytes [23]. Under the stimulation of the IL-4 and IL-13, M2 macrophages release a large amount of pro-fibrotic mediators such as TGF-β and platelet-derived growth factor (PDGF) to induce continuous fibroblast activation and to promote myofibroblast proliferation (Fig. 1). Furthermore, this type of activated macrophages binds to collagen type 1 (COL1) via β2-integrins and scavenger receptors, releasing the CCL18 cytokine that in turn promotes collagen production, which creates a self-amplifying loop [24]. Despite the efforts to elucidate the role of innate immune cells in fibrosis pathogenesis, several aspects have to be discovered, yet. Recently, Morse et al. using single-cell RNA-sequencing (scRNA-seq) have identified a novel population of pro-fibrotic macrophages that express at high levels the secreted phosphoprotein 1 (SPP1) genes (SPP1hi) [25]. The SPP1 gene encodes for osteopontin that has been discovered within the fibrotic foci. Extracellular osteopontin promotes monocyte/macrophage proliferation and fibroblast activation supporting the pivotal role played by $SPP1_{hi}$ macrophages in fibrosis progression (Fig. 1) [26].

2.2.2. Monocytes

Blood-derived monocytes play also a pivotal role in the development of fibrosis [27]. Interestingly, Satoh et al. have recently revealed the involvement of a specific subpopulation of monocytes in PF defined segregated-nucleus-containing atypical monocytes (SatMs) [28]. These monocytes are characterized by the expression of specific markers (Ceacam1 + Msr1 + Ly6C − F4/80 − Mac1 +) and present a bilobed nucleus. Interestingly, they demonstrate the unique role of these cells in the initiation of the fibrotic process but not in the control of inflammation. The same authors also reveal an intriguing mechanism at the basis of SatMs recruitment in lung fibrotic regions [29]. The insurgence of endothelial/epithelial lung injury causes the assembly of nuclear exosomes in the cells also called paraspeckles that are critical in the repair of damaged DNA preventing cell apoptosis. The formation of these paraspeckles is mediated by a specific long non-coding RNA (lncRNA). The authors reveal the pivotal role of the RNA-binding motif protein 7 (Rbm7) in mediating the degradation of this specific lncRNA impairing the paraspeckle formation. The lack of these paraspeckles causes caspase-3 activation in airway epithelial cells that release the C-X-C motif chemokine ligand 12 (CXCL12), which acts as a potent chemoattractant to SatMs (Fig. 1) [29].

2.2.3. Innate lymphoid cells (ILCs)

Monocytes are not the unique type of infiltrating cells upon the endothelial and epithelial release of TGF-β and chemoattractant mediators. Indeed, the infiltrating cells consist of monocytes, B cells, T cells, and innate lymphoid cells (ILCs) [30]. ILCs, specifically the type 2 (ILC2s), are recruited by the IL-33 and IL-25 released by injured epithelia [31,32]. They have been implicated in lung fibrosis due to their production of pro-fibrotic mediators first of all IL-13 but also IL-6 and IL-9 [31,33]. IL-13 has been demonstrated as one of the major drivers of fibrosis in the lung [34]. Indeed, it has been proposed as a target for IPF treatment; unfortunately, the clinical trials targeting IL-13 signalling failed to report positive effects, demonstrating the need to better elucidate the intricate effects of this and other cytokine cascades [35]. IL-13 is released by ILCs but it is mainly derived from T cells that are polarized to T-helper 2 (TH2) phenotypes in lung fibrotic lesions [36]. IL-13, together with the IL-4 released by TH2 cells, promotes the M2 polarization of macrophages [27].

2.2.4. Neutrophils

In the last years, neutrophils have attracted great interest in the field of lung disease. Neutrophils are myeloid leukocytes playing a key role in the fight of a wide range of pathogens. Different stimuli can activate neutrophils causing: i) phagocytosis, ii) release of granules (that contain proteases and ROS), iii) release of neutrophil extracellular traps (NETs). NET generation has been defined NETosis and it is a peculiar type of neutrophil cell death, even if some authors report that cells do not necessarily die after the release of NETs [37,38]. Upon activation, neutrophils release the NETs that are primarily composed of DNA decorated with histones and granule proteins such as lactoferrin, cathepsins, neutrophil elastase (NE), myeloperoxidase (MPO), and peptidylarginine deiminase type IV (PAD4) [39]. Diverse stimuli trigger NET formation such as bacterial/viral proteins, pro-inflammatory cytokines (TNF-α, IL-8, and IL-1β), and chemical (phorbol 12-myristate 13-acetate, PMA) [40]. The complex machinery regulating NET formation is still unclear. Several studies reveal that NETosis is dependent on the generation of ROS by NADPH oxidase 2 (NOX2). However, a NOX-independent mechanism has been proposed, in which the increase of intracellular calcium concentration is required instead of ROS [41,42]. Although NETs play a beneficial role as the primary defence from pathogens, protracted inflammation, cell damage, and prolonged viral infection may cause sustained activation of this process leading to tissue injury and pathological conditions. IL-8 is the major known chemoattractant for neutrophils in humans (Fig. 1) [43]. However, the research on these aspects is still ongoing and recently, Leslie et al. also reveal the role of formyl peptide receptor 1 (FPR-1) for neutrophil recruitment and PF progression [44]. NETs have been found in cystic fibrosis, acute lung injury, and lungs infected with bacteria, viruses, or fungi, in ARDS and fibrosis [45]. NETs have been detected in the sera of COVID-19 patients and correlated with both disease progression and thrombosis [46,47]. Recently, Khawaja et al. demonstrated that the hypoxic condition and HIF-1α upregulation may augment neutrophil recruitment and activation within the lung interstitium. Of note, in both PF and COVID-19, a progressive loss of lung functionality is evidenced that can lead to hypoxia phenomena sustaining the vicious loop of neutrophil activation [48].

Overall, in the last decades, several efforts have been done to elucidate the role of immune cells in the pathophysiology of lung fibrosis; however, further attempts are required to better understand how these new phenomena discovered in recent years can affect the initiation and progression of fibrosis. For example, the extracellular traps (ETs) are not exclusive of neutrophils. Recently, the ability of other types of immune cells to release ETs has been evidenced such as macrophages extracellular traps (METs) and eosinophils extracellular traps (EETs) [49,50]. To our knowledge, the role of these ETs in lung pathologies has remained unexplored, yet.

2.3. Myofibroblast differentiation: epithelial/endothelial-mesenchymal transitions and lipofibrogenesis

As reported above, the inflammatory process and immune activation are followed by the initiation of ECM deposition driven by a peculiar type of cells: the myofibroblasts, firstly described by Gabbiani et al. Myofibroblasts are characterised by a morphology similar to “conventional tissue fibroblasts”, produce components of ECM, and have a contractile capacity as smooth muscle cells [51]. During the last decades, several researchers have highlighted the complexity of mechanisms driving their formation and the cell types contributing to their origin. The myofibroblast origin in lung fibrosis is still debated, among other the main sources are: 1) alveolar epithelial cells that undergo an

epithelial-to-mesenchymal transition (EMT); 2) endothelial cells that undergo an endothelial-to-mesenchymal transition (EndMT); 3) fibroblasts that derive from peripheral blood fibrocytes and resident lung fibroblasts that become activated, a process defined fibroblast to myofibroblast transition (FMT); 4) pericytes and mesenchymal stem cells (bone-marrow-derived and Gli1 positive perivascular MSCs) (Fig. 2) [10,11].

2.3.1. Epithelial-mesenchymal transition in PF

EMT is a reversible process in which epithelial cells lose progressively the epithelial phenotype and acquire mesenchymal markers. EMT has been implicated in embryogenesis, normal and pathological wound healing, cancer metastasis, and organ fibrosis [52]. During the process, epithelial cells down-regulate E-cadherin and the miRNA200 family progressively losing apical-basal polarity. In parallel, they up-regulate mesenchymal markers such as fibroblast-specific protein 1 (FSP1), α-smooth muscle actin (α-SMA), COL1, vimentin, and fibronectin. The orchestration of this complex process is regulated by specific transcription factors defined EMT transcription factors (EMT-TFs), including Snail, ZEB, Slug, and TWIST. Regarding the involvement of EMT in lung fibrosis, several authors demonstrated the ability of alveolar epithelial cells (AECs) to transdifferentiate into myofibroblasts and develop fibrotic tissue both in vivo and in vitro [53–56]. Despite several decades of research and demonstration in cellular models, the contribution of epithelial cells to the bulk of myofibroblasts in lung fibrosis remains debated.

Upon lung injury, TGF-β, the major actor in EMT induction, is released not only by injured epithelial and endothelial cells but also by monocytes, macrophages, T-cells, and fibroblasts, leading to a self-sustained pathological loop. TGF-β binds to a heterodimeric tyrosine kinase receptor (composed of the type I and type II TGF-β-Receptor subunits), activating a plethora of different downstream pathways. The "canonical" TGF-β signalling pathway involves the activation of small mother against decapentaplegic (SMAD) proteins, which are a family of transcriptional activator proteins. The canonical TGF-SMAD signalling has been widely related to the induction of EMT in epithelial cells [57]. Apart from SMAD signalling, TGF-β can also signal through "non-canonical", non-SMAD pathways such as mitogen-activated protein kinase (MAPK), extracellular-signal-regulated kinase (ERK), JUN N-terminal kinase (JNK) as well as RHO-associated kinase (ROCK), and AKT pathways [58]. Similar to the canonical-SMAD signalling, the activation of pathways such as ERK can modulate the EMT induction promoting the exacerbation of fibrotic lesions [57]. TGF-β has been also related to EMT due to its crosstalk with the canonical Wnt/β-catenin pathway [59]. In fact, TGF-β promotes the accumulation of β-catenin in the nucleus inducing EMT in alveolar epithelial cells (Fig. 2)[60].

The Wnt/β-catenin signalling is another core pathway in fibrosis. Wnt is a family of proteins able to bind frizzled (FZD) receptor; based on the effector, Wnt signalling pathways can be defined as "Wnt/β-catenin canonical pathway" if it promotes the β-catenin accumulation, and "non-canonical pathways" if other intracellular pathways are activated (e.g. the planer cell polarity (PCP), JNK, protein kinase C/calcium (PCK/Ca2+) and others) [61]. Due to its effects and its cross-talk with the TGF-β signalling, Wnt/β-catenin signalling has been related to the progression of IPF [62]. Its activation promotes the EMT of epithelial cells, causes pulmonary fibroblast proliferation, and ECM deposition. Finally, Wnt/β-catenin signalling has been related to airway small muscle (ASM) cell proliferation and airway remodelling [63]. Several other receptors and intracellular pathways have been related to the induction and modulation of EMT processes. Among the others, Hill et al. reported the molecular mechanism that links autophagy with the induction of EMT of alveolar epithelial cells, corroborating its role in lung fibrosis and other pulmonary pathology [64,65].

2.3.2. Enothelial-mesenchymal transition in PF

Similar to the epithelial cells, endothelial cells undergo transdifferentiation into myofibroblasts in a process defined EndMT. During the transformation, endothelial cells decrease the expression of specific endothelial markers such as platelet endothelial cell adhesion molecule (PECAM), vascular endothelial cadherin (VE-cadherin), and increase the expression of mesenchymal markers FSP1, α-SMA, COL1, vimentin, and fibronectin [66]. In IPF, the activation of EndMT has been evidenced as a source of collagen-producing myofibroblasts [67]. Considering the EMT and EndMT similarity, they also share the role of various growth and pro-inflammatory factors in their induction with a central role of the TGF-β, Wnt/β-catenin pathways, and PDGF pathways [68]. More recently, the onset of new technologies such as scRNA-seq opens the way to a better definition of the mechanisms underlying this dynamic process. Jia et al. have discovered galectin-3 as a regulator of EndMT using this innovative approach [69], thus corroborating its causal role in fibrosis [70]. Galectin-3 is a protein that behaves as a pattern recognition receptor (PRR) playing a role in the recognition of microbial "pathogen-associated molecular patterns" (PAMPs), such as constituents of the bacterial and fungal cell wall, or viral genome [71]. The results of Jia et al. have identified a new molecular mechanism involved in EndMT, constituting a possible future target for fibrosis therapy (Table 1, Fig. 2). Of note, EMT and EndMT are bidirectional processes and a partial transformation has been evidenced further expanding the complexity of the related scenario in vivo [72].

2.3.3. Fibroblast to myofibroblast transition

Fibroblasts are another well-known source of myofibroblasts. The cell damage and the release of inflammatory cytokines and growth factors from macrophages and T-cells (e.g. IL-6, TNF-α, and TGF-β) drive the activation of resident fibroblasts expressing high-affinity type 2 TGF-β receptor that assumes spindle shape and starts to produce collagen. This process has been defined FMT and it is an essential process in wound healing and is driven by microenvironment stimuli as well as by the modification of the ECM composition and stiffness [73]. Several decades of research highlight the involvement of several signalling pathways able to modulate fibroblast proliferation and differentiation, such as PDGF signalling. PDGF has four isoforms that bind two PDGF receptor tyrosine kinases (PDGFR α and β). These receptors are highly expressed in fibroblasts and myofibroblasts where they prompt survival, proliferation, and migration following the release of their endogenous ligand PDGF. PDGF also synergizes with TGF-β promoting its release from activated alveolar macrophages and epithelial cells, thus crucially contributing to the self-activating loop of fibrosis spread [74]. Alongside the PDGFR tyrosine receptors, fibroblast growth factor (FGF) tyrosine kinase receptors (FGFR) play a central role in the activation of fibroblasts. High expression levels of FGFR-1 and FGFR-2 are found in several lung cell types (epithelial, endothelial, and myofibroblast-like, as well as interstitial cells) of IPF patients, where they crucially contribute to collagen synthesis and deposition driven by FGF-2 (Fig. 2)[75].

Once the injury is resolved, the fibroblast and myofibroblast activation must be switched off to prevent pathological conditions. Specifically, myofibroblasts can return to fibroblast phenotype, alternatively, they can initiate self-clearance via apoptosis [76]. The evasion from these mechanisms leads to the sustainment of fibrotic processes. Thus, several efforts have been recently made to better understand the mechanism that can cause the lack of myofibroblast deactivation. Among others, the inhibition of autophagy can not only promote the EMT processes but can also provide resistance to apoptosis in fibroblasts and myofibroblasts. The PI3K/AKT/mTOR activation reduces autophagy making fibroblasts and myofibroblasts resistant to apoptosis in IPF [77]. Similarly, the inhibition of eEF2K and p38 MAPK signalling decreases autophagy processes that in turn reduce lung fibroblast apoptosis [78]. In correlation with the autophagy decrease, ageing has arisen as a modulator of fibroblast activation and deactivation. In fact, Caporarello et al. demonstrate that lung fibroblast activation is transient in young mice but more persistent if compared with aged ones [18].

Table 1
List of the main innovative therapeutic approaches in preclinical or clinical testing for IPF treatment. Treatments explored for PF resulting from COVID-19 are also reported. Therapies that already proved to be ineffective or detrimental have not been included in this list, but can be found elsewhere [165,207]. For each therapeutic option, the name and typology of product, the molecular target, the data supporting efficacy, and, where available, the information about clinical trials started (type, name, and/or ClinicalTrials.gov identifier) are reported.

Name and type of the product	Target	Evidence of efficacy for IPF treatment (pre-clinical cellular, preclinical-animal, clinical)	Info about clinical trial	Clinical Application	Related references
Pamrevlumab, FG-3019 (humanized monoclonal antibody)	CTGF (connective tissue growth factor)	Clinical	Phase II completed (NCT01890265) Phase III ongoing (NCT03955146) Phase II ongoing (NCT04432298)	IPF PF in COVID-19	[208]
Ianalumab, VAY736 (humanized monoclonal antibody)	BAFF-R (B cell activating factor receptor)	Clinical	Phase II ongoing (NCT03287414)	IPF	[121]
Lebrikizumab (humanized monoclonal antibody in monotherapy or in combination with pirfenidone)	Interleukin 13 (IL-13)	Clinical	Phase II ongoing (NCT01872689)	IPF	[209]
Meplazumab (humanized monoclonal antibody)	CD147	Clinical	Phase II ongoing (NCT04275245)	PF in COVID-19	[210]
Losartan (small molecule antagonist)	Angiotensin II type 1 receptor	Clinical	Phase II ongoing (NCT00879879)	IPF PF in COVID-19	[211212]
PRM-151 (human recombinant protein)	Pentraxin-2 (PTX-2)	Clinical	Phase II completed (NCT02550873) Phase III ongoing (NCT04552899)	IPF	[125]
IW001 (oral immunotherapy)	Col(V) collagen autoantibodies	Clinical	Phase I completed (NCT01199887)	IPF	[213]
Brazilian green propolis (natural compound)	Various targets	Clinical	Phase II completed (NCT04480593)	PF in COVID-19	[214]
GB0139 (other name TD139) (small molecule inhibitor)	Galectin-3	Clinical	Phase I-IIa completed Phase IIb ongoing (NCT03832946)	IPF	[215]
CC-930 and CC-90001 (small molecule inhibitors)	JNK	Pre-clinical (animal) Clinical	Phase I completed Phase II ongoing (NCT03142191)	IPF	[216217]
BMS-986278 (small molecule inhibitor)	LPA1	Pre-clinical (cellular, and animal) Clinical	n.d. Phase II ongoing (NCT04308681)	IPF	[218]
GLPG1690 (small molecule inhibitor)	Autotaxin (ENPP2)	Clinical	Phase IIa completed (NCT02738801)	IPF	[219]
Saracatinib (small molecule inhibitor)	Src tyrosine kinase	Clinical	Phase Ib/IIa ongoing (NCT04598919)	IPF	[220]
Talagedib, ENV-101 (small molecule inhibitor)	Hedgehog pathway	Clinical	Phase II ongoing (NCT04968574)	IPF	n.d.
ORIN1001 (small molecule inhibitor)	IRE1α/XBP1	Clinical	Phase Ib ongoing (NCT04643769)	IPF	n.d.
Colchicine (small molecule inhibitor)	Inflammasome machinery	Clinical	Phase 3, randomised, double-blind, completed Phase 4, ongoing (NCT04818489)	PF in COVID-19	[221]
MSC (mesenchymal stem cell) therapy	ATII-cell intratracheal transplantation	Clinical	phase Ib.	Moderate/ Progressive IPF	[222]
Bone-marrow MSC	intravenous infusion	Clinical	Phase I/IIa ongoing (NCT02594839)	IPF	[129]
Lung Spheroid Stem Cells (LSCs)	intravenous infusion	Clinical	Phase I ongoing (NCT04262167)	IPF	n.d.
siRNA TRK-250	TGF-β1	Clinical	Phase I ongoing (NCT03727802)	IPF	[223]
siRNA nanoparticle and prostaglandin2	MMP3, CCL12, and HIFα mRNAs	Pre-clinical (animal)	n.d.	IPF	[224]
siRNA liposome	SART1	Pre-clinical (animal)	n.d.	IPF	[225]

2.3.4. Lipofibroblast formation

Myofibroblast deactivation can be obtained also by de-differentiation induction that is controlled by mitogen(s)/ERK/MAPK/CDKs, as opposed to TGFβ1/ALK5/MyoD signalling that drives fibroblast differentiation [79]. Recently, it has been proposed that myofibroblasts de-differentiate into another different type of fibroblast: the lipofibroblasts. Lipofibroblasts are lipid-droplet-containing interstitial fibroblasts rich in neutral lipids that support the maintenance of AT2 cell homeostasis as well as their protection against oxidative stress [80]. Lipofibroblast cells express the adipose differentiation-related protein (ADRP), peroxisome proliferator-activated receptors-gamma (PPARγ), and parathyroid hormone receptor (PTH1R). This de-differentiation can be transient, in fact, El Agha et al. have elegantly demonstrated that lipofibroblasts serve as a source of activated myofibroblasts in lung fibrosis. The presence of high levels of TGF-β activates the canonical TGF-β/SMAD pathway supporting the lipofibroblast-to-myofibroblast transdifferentiation. The authors also prove that PPARγ signalling is involved in the reversal of this event (Fig. 2). Of note, PPARγ expression is downregulated in IPF lung biopsy, likely due to hyperactive TGF-β signalling [81].

2.4. Inside the extracellular matrix deposition

The plethora of mechanisms described above has as main consequence the deposition of ECM that in turn modulates the myofibroblast formation in a self-amplifying activation loop. In the era of omic sciences, the study of the "matrisome" has considerably accelerated the discovery of mechanosensor mechanisms of extracellular stiffness. The matrisome includes all the genes encoding structural ECM components and ECM-associated components [82]. The increase of stiffness and an excessive lung stretch activates different signalling pathways implicated in the mechanical transduction, including Rho/Rho-associated protein kinase (ROCK), myocardin-related transcription factor-A (MRTF-A), and yes-associated protein 1 (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signalling pathways. The increase of stiffness mediates the Rho-mediated actin polymerization that results in myocardin-related transcription factor A (MRTF-A) nuclear translocation causing the increase of α-SMA and COL1 gene expression and promoting the fibroblast-to-myofibroblast transformation. Similarly, Rho induction of YAP/TAZ nuclear translocation promotes the gene expression of ECM genes such as PAI-1, connective tissue growth factor (CTGF), and COL1 [83].

The connective tissue stiffening directly drives the progression of fibrosis too, by controlling the integrin-mediated activation of latent TGF-β1 that, upon activation, promotes myofibroblast formation [84]. Finally, it has been evidenced that a stiff microenvironment is critical to enable TGF-β1 activation of non-canonical pathways such as focal adhesion kinase (FAK) and YAP/TAZ signalling [85].

2.5. Genetic and epigenetic modifications involved in fibrotic process

Several genetic modifications have been related to fibrosis susceptibility thank to the onset of genome-wide association studies (GWAS). The main genetic risk factors have been recently reviewed by Michalski et al. [86]. For example, the rs35705950 single nucleotide polymorphism (SNP) in the promoter region of mucin 5B (MUC5B) has been linked to increased risk of IPF as well as of other ILDs associated with rheumatoid arthritis and chronic hypersensitivity pneumonitis, too [87]. The MUC5B encodes a precursor protein that contributes to airway mucous production and has an important role in bacterial host defence; thus the MUC5B SNP leads to altered related protein production in the bronchiolar epithelium [88]. Mutations in genes responsible for telomere shortening (e.g. TERT, TERC, RTEL1, and PARN) and genes associated with surfactant dysfunction (SFTPC and SFTPA2) have been related to the progression of IPF, too [89,90].

The genetic modifications alone are not sufficient to explain the fibrosis progression. Indeed, epigenetic alterations can contribute to the activation of fibroblasts and EMT processes. In the last decades, several authors report the involvement of micro RNA (miRNA) in one or more mechanisms of lung fibrosis from the EMT, EndMT induction, and ECM production ending to the activation of immune cells [91–94]. Recently, other types of non-coding RNAs, the lncRNAs, are attracting great attention. lncRNAs can act as competing endogenous RNAs (ceRNAs), thus causing the inhibition of miRNA activity. In the attempt to discover possible targets to reduce the fibrotic process, LncRNA ZEB1-AS1, LncRNA MALAT1, and LncRNA-ATB have been reported to enhance the EMT process. As expected, these LncRNA silence the expression of specific miRNA, miR-141-3p/ZEB1, miR-503, and miR-29b-2 and miR-34c, respectively, which regulate the expression of proteins involved in EMT [95–97].

The highly complex regulatory network of circular RNA (circRNA)/miRNA/mRNA has been emerging as another important epigenetic control of fibrosis. However, to date, little is known about the effects of circRNA in lung fibrosis compared with lncRNA and miRNA. Only a few reports investigate the expression and the processes influenced by circRNA [98,99] demonstrating the need for further investigation in this field.

2.6. Extracellular vesicles and fibrosis process

Considering the mechanisms of cell-cell communication, peculiar carriers of signal molecules, miRNA included, are the extracellular vesicles (EVs). During the last decades, several authors have tried to elucidate the role of these particles in the pathophysiology of lung fibrosis [100]. EVs are a class of particles that can be divided into exosomes (EXs), microvesicles or microparticles (MPs), and apoptotic bodies based on their dimension and biogenesis [100–102]. EVs can load different cargos and based on their origin and production stimuli can produce different effects in recipient cells. Xie et al. have demonstrated that EXs released from pulmonary vascular endothelial cells in a mouse model of bleomycin-induced PF have lower let-7d miRNA levels. The authors demonstrate that this reduction drives the stimulation of pericyte transdifferentiation and fibrogenesis through the TGFβRI/FoxM1/SMAD/β-catenin pathway [103]. Similarly, human lung epithelial cells release EVs enriched with miR-21when fibrosis is induced with arsenite. The miR-21-enriched EVs are transferred into fibroblasts where they activate the PTEN/AKT signalling pathway promoting glycolysis-related myofibroblast differentiation [104]. In this scenario, also macrophages are able to secrete EVs with different cargo based on the received stimuli. EXs derived by silica-induced macrophages have high levels of both SPP1 and miR-125a-5p that can promote myofibroblast differentiation when transferred to fibroblasts [105,106].

EVs have been also proposed as a therapeutic option for different pathologies. Indeed, EVs loaded with specific miRNAs, lncRNAs, and RNA Piwi-interacting (piRNA) can modify the response of recipient cells by targeting key cellular and molecular players in lung fibrosis. However, the research in this field is still mostly at the pre-clinical level (Table 1), thus still far too soon translate into a clinical therapeutic option.

3. Approved and future therapeutic approaches to IPF

In agreement with the numerous molecular mechanisms described above, the identification of therapeutic targets in IPF has also revealed to be a long-lasting and complex process. Only two antifibrotic drugs, i.e. nintedanib and pirfenidone, have been so far approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat IPF. Both drugs have been demonstrated to slow down the decline in lung function and reduce the risk of acute respiratory exacerbations in patients with IPF [107,108]. Since their first approval in 2014, several clinical trials [109] and observational data [110] have supported the safety and efficacy of these two drugs, which provided a noteworthy amelioration of the IPF patient management. Importantly, these studies not only corroborate the efficacy of nintedanib and pirfenidone as IPF drugs, but also identify a series of potentially harmful (e.g., prednisolone, azathioprine, and warfarin) or ineffective (e.g. bosentan and acetylcysteine) drugs for IPF patients [90]. Considering that some of the harmful/ineffective drugs had constituted the standard of care for IPF only a few years before [111], it can be understood that the IPF treatment paradigm has totally changed since the 2010s.

Nintedanib is a small molecule inhibitor of multiple receptor tyrosine kinases (RTKs), namely the FGFR, PDGFR, and vascular endothelial growth factor receptor (VEGFR) [112]. It had been designed as a binder of the ATP-binding pocket of these RTKs and, similarly to most RTK inhibitors, and had been initially developed as a potential anti-proliferative and anti-angiogenic agent in cancer[113]. Interestingly, the separate inhibition of PDGFR, FGFR, and VEGFR, which was useful in pre-clinical studies, failed to slow down IPF progression in clinical trials, explaining why the research has begun to explore a multi-target therapeutic strategy [114].

On the other hand, pirfenidone is an orally administered pyridine with combined anti-inflammatory, antioxidant, and antifibrotic actions. Its clinical use has preceded by far the full characterization of its

mechanism of action, which is still nowadays not completely understood. Data obtained from cultured primary human lung fibroblasts have demonstrated that pirfenidone can inhibit fibroblast proliferation and attenuate TGF-β-induced expression of α-SMA and COL1, two crucial mediators of fibrosis [115]. More generally, this small molecule drug has been demonstrated to decrease TGF-β1, TNF-α, PDGF, and COL1 expression in several cell models, which was related to its ability to prevent or remove excessive deposition of scar tissue in several organs [116]. Furthermore, pirfenidone has been found to upregulate the gene expression of regulator of G-protein signalling 2 (RGS2), an endogenous anti-fibrotic protein present in pulmonary fibroblasts [117]. More recently, pirfenidone has been demonstrated to inhibit the phosphorylation of transmembrane mucin 1 (MUC1-CT) affecting the formation of a nuclear complex of phospho-SMAD3/MUC1-CT/active β-catenin necessary for the TGF-β1-induced fibrotic processes [118].

Despite the recognized advantage brought by the clinical use of pirfenidone and nintedanib, they are not able to revert the disease but only to decrease the rate of IPF progression [119], and thus they have been classified as disease-modifying therapies for IPF [90]. Long-term studies will be required and new clinical trials are currently recruiting patients to assess whether these drugs will slow IPF progression on the long time scale, thus providing a true benefit for life expectancy. At the moment, for both drugs, a trend in favour of a reduction in mortality is reported [110]. Meanwhile, new diagnostic and therapeutic options for IPF patients are actively being explored, as it has become clear that lung transplantation is not a sustainable solution [120].

Thanks to the discovery of new molecular mechanisms, innovative approaches designed on novel targets, including the use of monoclonal antibodies [121] and stem cell therapies [122], are being explored for IPF treatment, some of which are already in clinical testing. The most promising of these solutions is probably Pamrevlumab (FG-3019), a fully recombinant human monoclonal antibody raised against CTGF, a secreted glycoprotein acting as a common driver of fibrosis and cancerous conditions. Pamrevlumab already have passed a phase II clinical trial [199] and is currently undergoing a phase III clinical trial. Similarly, PRM-151 is a fully recombinant version of human serum amyloid P or pentraxin 2 (PTX2) protein [123] that holds great promise for IPF treatment. Unlike other therapies that work by blocking a single target downstream fibrotic signalling, this protein works by reversing and possibly healing the fibrotic tissue. It targets the immune system and, in particular, macrophages to turn off M2 polarization and reverse the process of fibrosis [124]. PRM-151 injected intravenously showed efficacy in IPF patients in a phase II trial [125] and has recently entered the phase III trial.

Recently, the use of autologous or allogenic stem cell transplantation has emerged as an innovative therapy to slow down IPF progression. Phase I clinical studies demonstrate the safety and some beneficial effects of MSCs derived by different tissue (e.g. placenta, adipose, and bone marrow) in patients with mild to moderate IPF [126–128]. The stem cells produce a large number of biologically active substances with anti-inflammatory, immunosuppressive, and angiogenic properties supporting their use as anti-fibrotic agents. The use of bone-marrow-derived MSC has been also translated in phase IIa clinical trials; the intravenous administration of a high-cumulative dose of stem cells proves to slow down the lung function decline in IPF patients [129]. Most recently, the use of a heterogeneous population of lung spheroid stem cells (LSCs) has been proposed in a pre-clinical rat model of PF [130]. This peculiar type of cells expresses the progenitor markers (cluster of differentiation 90, CD90, cluster of differentiation CD105, CD105, surfactant protein C, SFTPC, club cell secretory protein, CCSP, and aquaporin 5, AQP 5) and derived by a specific three-stage adherence-suspension-adherence culture method that from tissue biopsy generates three-dimensional (3D) cell agglomerations in suspension, termed lung spheroids (LSs). The ability of an intravenous infusion of LSCs to reduce the progression of fibrosis in the rat model has opened the way to the translation in Phase I clinical trial that is still ongoing (ClinicalTrials.gov, identifier NCT04262167).

These and other significant examples of advanced IPF therapies are summarized in Table 1. Noteworthy, some of them are currently being investigated also as potential therapy of PF resulting from COVID-19. In this regard, it is worth noticing that also pirfenidone and nintedanib are currently undergoing a phase II (ClinicalTrials.gov, identifier NCT04607928) and III (ClinicalTrials.gov, identifier NCT04541680) clinical trial, respectively, for the treatment of SARS-CoV-2 induced PF.

4. What about the lung lesions in post-COVID-19 patients?

Infectious agents (i.e. bacteria and viruses) have emerged as one of the causes of PF development for several years [131]. Recently, the SARS-CoV-2 has further supported this hypothesis. The SARS-CoV-2 is a positive-sense single-stranded RNA virus [132] associated with extensive lung involvement, in the worst cases represented by ARDS, that can be complicated by PF, due to the substantial fibrotic consequence of infection [133,134].

Although the infection by SARS-CoV-2 can be eradicated in numerous cases, the consequent development of pulmonary fibrotic complications cannot be precluded [135]. About 40% of patients with COVID-19 develop ARDS, in some cases resulting in lung fibrosis as a long-term outcome [136]. PF occurs more frequently in patients with severe or critical COVID-19 [134]. Recently, some risk factors leading to the development of severe SARS-CoV-2 infection have been identified including age, smoking status, ethnicity, and male sex. In addition to these risk factors, some comorbidities contribute to increasing hospitalization and mortality in COVID-19 disease, like a chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and obesity [137]. Also, the transcriptome analysis of cells derived by patients with chronic lung diseases revealed the higher levels of genes linked directly to the efficiency of viral replication and to an improved inflammatory microenvironment supporting the susceptibility of these subjects to severe COVID-19 infection [137]. Conversely, the home use of drugs able to control cholesterol such as statins and anti-diabetic drugs such as metformin have been evidenced to lower the risk of death of COVID-19 patients[138,139].

Recent literature data have confirmed that COVID-19-associated fibrotic alterations are still persistent after 4 and 6 months from COVID-19 symptoms onset [140,141] and in some cases they are not resolved in the first year following the virus infection [142]. The insurgence of the fibrotic lesions is mainly associated with older age, ARDS, longer hospital stays, tachycardia, mechanical ventilation, and higher initial chest CT score [141]. More in general, Marvisi et al. have highlighted that among COVID-19 patients, more than one out of three developed fibrotic lesions, with prevalence in patients displaying the same comorbidities, including hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and chronic renal failure [143].

Of note, the severity of residual functional or imaging pulmonary abnormalities, as well as the probability of residual scar, is strictly linked to the SARS patient's age [144], seeing as aging confers a profibrotic and irreversible senescent phenotype to fibroblasts [145,146].

Recently, Solomon et al. have reviewed the main papers about post-acute lung complications of COVID-19 [147]. They have summarized the etiology of lung fibrosis after COVID-19 in different mechanisms: i) known consequence of ARDS; ii) effects of mechanical ventilation with direct injury of lung alveoli; iii) improved response to fibrotic stimuli due to virus damage; iv) direct virus induction of fibrosis.

In a small subgroup of patients, post-COVID-19 fibrosis has been related to an exacerbation of underlying ILD. Interestingly, these results were derived by a follow-up no longer than 6 months, and data concerning the long-term impact of COVID-19 infection on lung health are still lacking. The fibrotic disease resulting from virus dependent-ARDS has been already investigated for other coronaviruses, i.e. middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV) infections, for which the

onset of lung fibrosis has been reported to occur to a similar extent to SARS-CoV-2 (33% and 27.8–62% of patients, respectively) [6]. In particular, SARS-CoV patients have lung interstitial abnormalities and functional decline that are recovered over the first 2 years after infection and then remained stable; of note, in 4.6% of survivors, the alterations persisted after 15-year follow-up long-term studies [135,148].

COVID-19 pathogenesis is characterized by the stimulation of adaptive immunity after the early infection and respiratory dysfunction resulting from lung injury and hypoxemia. The disease results in a local cytokines storm and systemic hyperinflammation phase [149,150]. Indeed, several pathological features of COVID-19 patients are shared with PF such as the epithelial alterations and diffuse alveolar damage (DAD), impairment of vascular and microvascular systems with the presence of microthrombi, acute fibrinous pneumonia, ECM accumulation, and activation of the immune system with persistent inflammatory processes. Generally, epithelial and vascular alterations occur in the early infection, while fibrotic features arise after 3 weeks from the onset of the symptoms [151].

The key factors that mediate the profibrotic processes in response to coronaviruses infection, especially to SARS-CoV-2, are currently unknown, but surely an innate immune response, altered gene expression profile in myeloid population, hyperactivation of alternatively activated macrophages, and high level of proinflammatory and profibrotic factor production contribute to the lung pathological processes [6]. Indeed, from a molecular point of view, the lung inflammation caused by SARS-CoV-2 infection has been related to the infiltration of immune cells into the lung with the resulting development of lung hyperinflammation and fibrosis [152,153]. The fibrotic event results from the excessive macrophage activation that occurs in severe COVID-19 patients, thus leading to dysregulation of mechanisms involved in the tissue repair [154]. Interestingly, it is now clear that the deadly COVID-19 infection is defined by two main patterns: a lung high viral load and cytokine expression with limited morphological alterations or low viral load and cytokine expression with elevated numbers of immune cells [155].

The mechanisms by which COVID-19 infection mediates PF seem to partially overlap those already reported for PF in paragraph 2.2, in particular concerning the role of epithelial cells: basically, the alveolar epithelial cell injury leads to fibroblast infiltration and activation/release of pro-fibrotic mediators such as TGF-β and PDFG with the consequent ECM synthesis and accumulation [156]. Specifically, once the damage occurs in the lung, AT2 cells express and release numerous growth and fibrogenic factors as well as cytokines, including monocyte chemoattractant protein-1 (MCP-1), TGF-β1, TNF-α, IL-1β, and IL-6. Subsequently, these factors stimulate hyperproliferation of AT2 cells, recruit fibroblasts to the fibrotic loci, and induce *trans*-differentiation/activation of fibroblasts into myofibroblasts, leading to alveolar function loss, especially concerning alveoli-capillaries gas exchange [157,158].

However, these mechanisms implicated in PF are not specifically triggered by viral infection. On the contrary, some recent evidence have highlighted possible characteristic mechanisms by which SARS-CoV-2 infection leads to PF onset. One of these is focused on the role of angiotensin-converting enzyme-2 (ACE2), the pivotal enzyme necessary for the binding and entrance of SARS-CoV-2 into the host cells [159]. Indeed, genetic as well as acquired factors, such as chronic lung disease, diabetes, heart failure, and the use of ACE inhibitors, lead to increased expression of ACE2 in target organs. Since the expression of ACE2 increases susceptibility to SARS-CoV-2 infection, all these factors are associated with a predisposition to COVID-19 infection [160,161]. The major sources of ACE2 are AT2 pneumocytes [162]. The viral infection has a cytolytic effect on AT2 cells, resulting in their differentiation toward AT1 pneumocytes together with their active proliferation, with the consequent replacement of AT2 pneumocytes that is associated with the pathogenesis of lung injury [163–166]. Furthermore, the SARS-CoV-2-mediated ACE2 internalization leads to a reduction of ACE2 on the cellular surface and the consequent increased angiotensin II (Ang II)/angiotensin 1–7 (Ang 1–7) ratio, the substrate and the product of ACE2, respectively [167]. To this regard, the renin-angiotensin-system (RAS) has been proven to be altered in COVID-19 patients as well as in IPF ones, since it is involved in acute lung diseases development, i.e. ARDS, mainly due to the implication of ACE2 [164,168], whose expression is altered in IPF lung fibroblasts [169]. The lack of ACE2 expression in ACE2-KO animals increases ARDS susceptibility, while the inactivation of ACE in ACE2-deficient mice attenuates ARDS [170]: indeed, ACE activity is increased in ARDS-lungs, while ACE2 activity is reduced [171,172]. Of note, SARS-CoV-2 infection leads to RAS imbalance and tissue damage by reducing ACE2 levels. In this context, RAS-blocking drugs (i.e. ACE inhibitors and angiotensin II receptor blockers) have been employed for COVID-19 treatment to restore the RAS balance [173]. In particular, there are different pathways related to the RAS axis: the ACE/Ang II/angiotensin II type 1 receptor (AT1R) pathway, i.e. "classical pathway", and ACE2/Ang (1–7)/Mas receptor (MasR) pathway, i.e. "non-classical pathways" [174], which are inversely correlated. The ACE/Ang II/AT1R axis mainly increases the inflammation (e.g. IL-1β, TNF-α, and IL-8), fibrosis (e.g. TGF-β and α-SMA), apoptosis, and ROS production, while the ACE2/Ang(1–7)/MasR axis decreases the phosphorylation of ERK1/2, c-Jun, MAPK, and SMAD family, mitochondrial damage, and ROS/NOS production [174]. Overall, the SARS-CoV-2-mediated depletion of ACE2 and Ang-(1–7) in tissues alters the balance of RAS axes, favoring the ACE/Ang II/AT1R pathway, which is manifested by the clinical characteristics of COVID-19, i.e. inflammation, oxidative stress, tissue injury, multi-organ dysfunction and coagulopathy [160,175,176]. Thus, the restoration of balanced RAS by ACE-2/Ang-(1–7)/MasR stimulation, as well as AT1R activation, could be a promising therapeutic approach. Interestingly, SMAD3 and ERK1/2 coordinately mediate the TGF-β-induced release of CTGF by fibroblasts. The crosstalk between SMAD3 and ERK1/2 plays an important role in regulating CTGF expression, i.e. in wound repair and tissue fibrosis, and could be exploited in therapeutic targeting of fibrotic conditions [177]. Indeed, TGF-β, together with CTGF/CCN2 and PAI-1, is a pro-fibrotic factor released in response to a lung injury. In particular, increased CTGF and TGF-β were found in the alveolar epithelial cells inoculated with SARS-CoV-2 [178], as well as elevated plasma tissue-type plasminogen activator (tPA) and PAI-1 levels were found in COVID-19 hospitalized patients and they were associated with worse respiratory status, indicating that fibrinolytic homeostasis in COVID-19 is complex with a subset of patients expressing a balance of factors that may favor fibrinolysis [179]. These data provide the rationale for the possible clinical use of Pamrevlumab, a monoclonal antibody against CTGF in patients with severe COVID-19 (Table 1).

Among the numerous activities in which TGF-β is implicated, the control of ECM synthesis/degradation as well as production/turnover of its components is critical, especially in pathological conditions such as IPF [180]. Indeed, the ECM changes attributed to IPF development have been related to ECM remodelling in COVID-19 patients [181,182]. In particular, since the fibrogenesis in IPF reflects an imbalance between synthesis and degradation of collagen, the matrix metalloproteinases (MMPs) degraded type I, III, and VI collagen, the MMPs degraded C-reactive protein (CRPM), and the type III and VI collagen formation have been found altered in COVID-19 patients, underling their putative role as useful markers to predict the PF development related to SARS-CoV-2 infection [181–183] and probably mediated by the TGF-β stimulation [184]. Among MMPs, MMP7 has been described as a main profibrotic metalloproteinase, which promotes a fibrotic response via regulatory effects on epithelial repair and release of latent TGF-β. Even if its role in PF has been considered pleiotropic, since it is implicated in apoptosis, inflammation, fibroproliferation, and innate immunity, a recently published study has demonstrated that plasma MMP7 measured at 9 weeks in severe COVID-19 survivors is strongly correlated with pulmonary function impairment [185].

Generally, since the ECM and ECM-related glycoprotein alterations are characteristic features of IPF, their involvement in the development of IPF starting from SARS-CoV-2 infection has been highly considered in

the last two years especially as putative biomarkers for the prediction of COVID-19 severe disease progression. For instance, one important biomarker for ILDs is represented by Krebs von den Lungen-6 (KL6), a glycoprotein classified as human MUC1 mucin: specifically, the MUC1 extracellular region contains the KL-6 epitope domain, which is cleaved from the cell surface in response to injury and released into the surrounding environment [186]. Indeed, increased concentrations of serum KL-6 have been correlated with lung epithelial damage, involved in interstitial lung disease including IPF, caused by damaged AT2 pneumocytes [187,188]. To this regard, it has been demonstrated that KL-6 concentrations were increased in COVID-19 patients with fibrotic lung alterations than in the non-fibrotic group; in particular, COVID-19 patients, who developed severe persistent fibrotic lung complications at HRCT, showed persistent high levels of KL-6 during the follow-up [189]. Thus, high concentrations of serum KL-6 in the early stage of COVID-19 should be highly taken into account for the early prevention of PF development [188].

The mucin MUC1 is expressed ubiquitously on epithelial surfaces and it has been considered as a key element in the host response to infection, particularly after the release of inflammatory cytokines such as IL-1β and IL-6 [190]. To this regard, elevated MUC1 mucin protein levels were found in airway mucus of critical ill COVID-19 patients [191] as well as interleukins [164], though no significant differences have been revealed in baseline levels of IL-1β, IL-6, and TNF-α between patients with COVID-19 and critically ill subjects with ARDS [192]. On the contrary, high levels of IL-18 were found in 85% of the COVID-19 patients that had ARDS and 78% of those that developed PF [193]. Further, levels of IL-13, one of the major factors implicated in lung fibrosis, have been demonstrated to be elevated in patients with severe COVID-19, underlining its ability in identifying COVID-19 patients who needed of mechanical ventilation [194].

Recently, the implication of NETs has been considered even concerning to SARS-CoV-2 infection, which seems to mediate NETosis. Several authors report the presence of NETs in the plasma and lungs of COVID-19 patients [195–198]. Interestingly, soluble and cellular factors triggering NETs were significantly increased in COVID-19 patients and pulmonary autopsies confirmed NET-containing microthrombi with neutrophil-platelet infiltration [195]. Generally, the cytokine storm and ARDS have been demonstrated to be promoted by NETs that play the main role in the interaction between neutrophils and macrophages during the early acute phase of acute lung injury [199]. Indeed, NETs contribute to acute respiratory failure in COVID-19 and the use of tools able to degrade NETs may reduce inflammation and improved oxygenation in patients [200]. However, the mechanisms regulating NET formation are currently unclear as is its implication in COVID-19-induced PF. SARS-CoV-2 generates NETs inducing NFκB pathway activation in alveolar epithelial cells that triggers the IL1β release with a consequent strong cytokine storm release and inflammatory event as well as increased ROS production. These events are more evident in older experimental animals than in younger ones, trying to explain the more severe progression of COVID-19 in older people [201,202]. Veras et al. deeply investigated the direct role of SARS-CoV-2 in NETs induction. They demonstrate that only viable but not inactivated viruses can promote a huge release of NETs in neutrophils. Interestingly, the ACE2/transmembrane Serine Protease 2 (TMPRSS2) pathway is crucial for SARS-CoV-2 entry and release of NETs [198]. Thus SARS-CoV-2–activated neutrophils contribute to tissue injury in COVID-19 patients and specifically promote lung epithelial cell death in vitro [198]. Furthermore, NETs can induce the EMT in lung epithelial cells, thus further supporting NET role in fibrosis pathogenesis [196].

Interestingly, the evaluation of blood NETs in COVID-19 patients has allowed discriminating survivor patients, i.e. a decrease of NETs formation from day 1 of admission to intensive care unit to day 3 was strongly correlated with survival after 28 days [203], underlying the pivotal role of NETs in the COVID-19 development and lung alterations. These data show off a possible crucial role of NETs in the pathophysiology of COVID-19 and the inhibition of NETs could represent a potential therapeutic target for COVID-19.

For certain, the lung alterations that occur as a consequence of SARS-CoV-2 infection are involved in the development of PF, and, even if the relative pathological mechanisms are not completely elucidated, possible pathways are proposed and schematically presented in Fig. 3.

Taking these data together, it is still premature to know whether lung changes occur as a temporary response to COVID-19 infection and they will spontaneously be resolved over time or rather they represent an irreversible pathological feature caused by the virus infection and they will persist in survivors patients. Surely, the data collected until now suggested that fibrosis persists for many months after the COVID-19 recovery in some patients [140,142]. Finally, whether the PF developed following COVID-19 infection is stable or progressive is still unknown, especially considering possible genetic, aging, and metabolic risk factors, and further investigations are needed [156].

5. Conclusions

PF is a complex and multifactorial pathology. For several decades, scientists have attempted to elucidate the molecular mechanisms involved in the initiation and propagation of fibrotic lesions. Despite the knowledge has been largely improved, several issues remain to be clarified. On the other hand, the recent pandemic has prompted the need to identify from scratch the mechanisms at the basis of COVID-19 disease progression as well as the characteristic features of the post-COVID lesions, in order to ameliorate the prognosis of millions of infected patients and also limit the effects after the infection is resolved. Thus, at this point, the question is: can the knowledge about pulmonary fibrosis teach how to handle COVID-19 and post-COVID-19 lesions or vice-versa? This question is not trivial to be solved. What is evident is that fibrosis and pulmonary lesions derived by SARS-CoV-2 infection share several mechanisms, namely i) an over-activation of the immune system; ii) the secretion of pro-inflammatory and pro-fibrotic cytokines; iii) epithelial and endothelial damage; iv) overproduction of ECM components; v) decreased lung functionality. The most obvious thought is that the bulk of information gained from the study and therapy of PF can be used to handle post-COVID-19 lesions when the progression of fibrotic lesion occurs. However, on the other hand, the impressive ability of SARS-CoV-2 to induce ARDS and fibrotic lesions has corroborated the idea that infective agents play a pivotal role in the initiation of PF, a pathology whose aetiology has long been thought to be mostly idiopathic. This may be explained by the fact that the initial lung injury can occur several years earlier than the insurgence of the clinical symptoms hampering the finding of a direct link between the presence of a viral infection and the PF. This pandemic has prompted the attention on this aspect, highlighting the importance to better understand the molecular dynamics of virus-lung cell (from epithelial to immune cells) interplay. This could lead to the discovery of new targets for the management of COVID-19 and post-COVID-19 patients and could be hopefully translated into the handling of PF, too.

Herein, the comparison of these two pathologies has certainly led to two other considerations. First, COVID-19 has stressed the correlation among lung infection, alveolar damage, and circular thrombosis [204]. In this context, scientists have acquired awareness of the causal role of neutrophils and their activation (NETosis) in the promotion of lung lesions, prompting the investigation of the role that this process could play in PF progression. This has also revealed the possibility to find new targets to cure or slow down COVID-19, post-COVID-19 lesions, and IPF. The second consideration regards the importance of age in the fibrotic process. Most of the COVID-19 patients that develop lung fibrosis lesions are elderly. This is not surprising considering that some authors highlight ageing as a key feature to discriminate between reversible or irreversible PF [18,205,206]. However, the pandemic has underlined this difference raising the need to investigate which mechanisms, probably related to immune system control, can switch off the process.

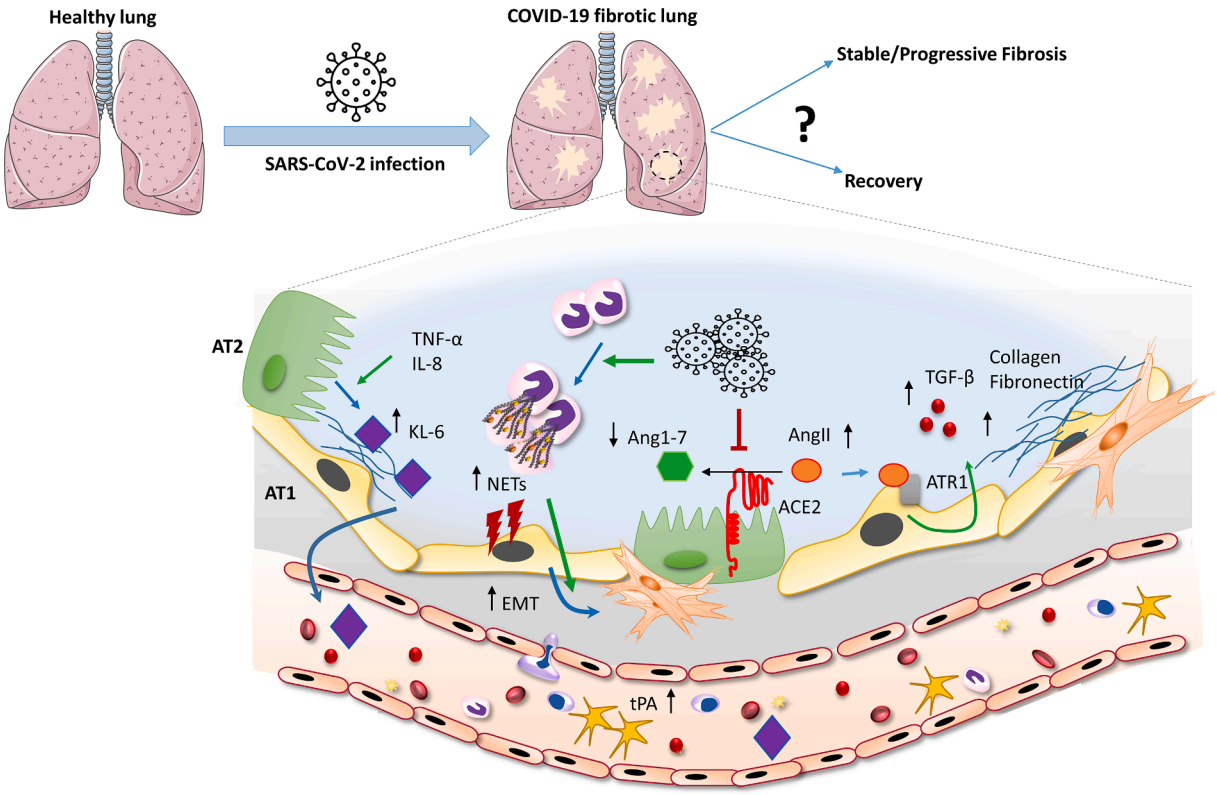

Fig. 3. Possible characteristic mechanisms of lung fibrosis induced by SARS-CoV-2 infection. The viral infection has a cytolytic effect on alveolar epithelial type II cells (AT2) cells (green cells), the major source of ACE2, resulting in the differentiation of AT2 toward alveolar epithelial type I cells (AT1) pneumocytes and in the increase of AngII, which binds to its receptor AT1R promoting the expression of pro-inflammatory factors such as cytokines as well as increased tPA accumulation in the blood. The pro-inflammatory molecules release contributes to ECM remodelling thus leading to fibrogenesis. The pro-inflammatory cytokines (TNF-α and IL-8) cause the release of KL-6 from AT2 cells. Virus prompts NET formation that in turn reinforce the epithelial damage (yellow cells) and promote the EMT process contributing to myofibroblast accumulation.

In conclusion, despite the impressive progress of these few years, multiple challenges need to be overcome to translate the knowledge into effective therapies for both fibrosis and COVID-19 lung lesions. The translation from bench to the bedside is possibly slowed down by a paucity of preclinical models able to recapitulate the heterogeneity of PF and also of effective clinical parameters and peripheral biomarkers able to stratify ILD and COVID-19 patients. Research has to try to close these gaps to drive the therapy in the new era of personalized medicine also considering that the number of people suffering from lung pathologies is expected to increase in the next future.

CRediT authorship contribution statement

Chiara Giacomelli: Writing – original draft, Writing – review & editing. **Rebecca Piccarducci:** Writing – original draft, Writing – review & editing. **Laura Marchetti:** Writing – original draft, Writing – review & editing. **Chiara Romei:** Writing – review & editing. **Claudia Martini:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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