EDITORIAL

Demystifying pulmonary fibrosis

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INTRODUCTION

This month, September, is Pulmonary Fibrosis Awareness Month, and this year, 2020, will be forever remembered as the year that brought us COVID-19. Pulmonary fibrosis and COVID-19 have more in common than at first seems apparent, and it is incumbent upon us to take what learnings we can from these two dreadful conditions to help us understand the shared mechanisms that will help us improve outcomes for people with progressive scarring conditions of the lung.

Both conditions start with lung injury: in the case of COVID-19 it can be very dramatic, leading to acute respiratory distress syndrome (ARDS), whereas in pulmonary fibrosis it is often insidious, and the originating injury is often unknown until it is too late. Both conditions exhibit their most severe consequences in elderly men, and indeed elderly men with pulmonary fibrosis are at particularly high risk of mortality from COVID-19 (15). Both are diseases that have been associated with the metabolic syndrome, namely, the constellation of hypertension, diabetes, and obesity. Finally, COVID-19 may directly lead to the development of pulmonary fibrosis through the direct consequences of virus-induced acute lung injury (ALI) or indirect consequences of the cytokine-mediated alveolar damage. If we understand the shared mechanisms that exist between these two conditions that characterize the extremes of lung injury and failing repair, we will be better able to deal with both the emerging epidemic of fibrotic lung disease and the very immediate COVID-19 pandemic.

MECHANISMS OF LUNG INJURY

The relationship between lung injury and fibrosis is well described; indeed, much of what is understood about the development of pulmonary fibrosis is based on data obtained from in vivo models of lung injury. In these models of pulmonary fibrosis lung injury is induced, often through inhalation of fibrogenic material such as bleomycin, FITC, or silica, which leads to an inflammatory phase, followed by a fibrotic phase and in many cases a resolving phase (26). Even in longer-term and more “clinically relevant” models such as radiation-induced lung fibrosis, there is an initial inflammatory phase lasting a few weeks with a long latent phase and then a very dramatic, nonresolving, fibrotic phase at between 5 and 6 mo (43). One of the key molecular mechanisms of lung injury and fibrosis triggered by many of these models is activation of epithelial transforming growth factor (TGF)-β1 (56), and indeed models of pulmonary fibrosis where active TGF-β1 is overexpressed in the lung with adenoviral gene transfer or transgenic overexpression can lead to progressive fibrosis without substantial inflammation (30, 52). A number of strategies targeting TGF-β1 activation have been used experimentally to inhibit both acute lung injury (ALI) (42) and fibrosis (22, 43), but global strategies have proved challenging because of the pleiotropic functions of TGF-β1, and its vital roles in inflammation and tumor suppression have led to insurmountable toxicity concerns. However, efforts to selectively inhibit TGF-β1 at sites of epithelial injury or by targeting fibroblast TGF-β1 activation have shown some promise, and indeed inhibitors of galectin-3, which inhibits fibroblast and macrophage TGF-β1 (33), are currently in phase II clinical trials (Clinical.Trials.gov: NCT03832946). However, it is clear that ALI is not by itself sufficient to lead to progressive fibrotic disease, as in many cases even the most severe ALI and ARDS can either resolve to some extent or at least not progress (8, 21), and there either needs to be the development of a self-amplifying (positive feedback) loop generating perpetually high levels of active TGF-β1, which promotes tissue fibrosis rather than repair, or the signals that switch off profibrotic pathways once the injury has resolved are defective. At least two such mechanisms have been identified, although there are likely many more. Recently, a polymorphism near the AKAP13 gene associated with high levels of AKAP13 mRNA expression in the lung has been identified to increase the risk of developing idiopathic pulmonary fibrosis (IPF) (2). A-kinase anchoring protein 13 (AKAP13) is a Rho guanine nucleotide exchange factor (GEF) that leads to RhoA activation, and therefore it is possible that patients with high levels of AKAP13 will have enhanced RhoA activation in response to injury, which in turn could amplify TGF-β1 activation; studies are currently ongoing to address this hypothesis (see Fig. 1). Similarly, it is well known that TGF-β leads to increased expression of the ITGB6 gene and α5β6 integrin expression, which in turn activates further TGF-β (54). Under normal circumstances this feedback loop is regulated by a number of transcription factors including the glucocorticoid receptor, progesterone receptors, and the transcriptional repressor ELK1 (55). Loss of ELK1 leads to enhanced ITGB6 expression, increased α5β6 integrin on the epithelium, and enhanced fibrosis both in response to lung injury (55) and in spontaneous fibrosis in aged Elk1-null mice (9) (see Fig. 1). It is interesting to note that ELK1 is an X-linked gene, and this might explain some of the sex imbalance seen in IPF. There is considerable work to be done to understand the molecular mechanisms that may amplify TGF-β, and other fibrotic mechanisms, after lung injury and whether targeting these amplification pathways will be sufficient to prevent the development of progressive fibrosis without affecting the important homeostatic functions of TGF-β.
An emerging role for TGF-\(\beta\) in COVID-19 has been described (58), and it would be surprising if TGF-\(\beta\) were not involved in the response to COVID-19-induced ARDS, given the known role of TGF-\(\beta\) in response to virus-induced lung injury (36) and the potential for SARS-CoV-2 to engage integrins through the RGD domain in its Spike protein (51). It is interesting to also note the pronounced sex imbalance in severe COVID-19 (17), and therefore understanding the role of its amplification factors including AKAP13 and ELK1 in COVID-19-related complications will be important.

**GENETICS, AGING, AND FIBROTIC LUNG DISEASE**

Pulmonary fibrosis is an age-related disease caused by epithelial injury to people with appropriate genetic susceptibility. Pulmonary fibrosis can occur without obvious cause, when it is called idiopathic pulmonary fibrosis (IPF), it can be caused by exposure to fibrogenic substances such as asbestos fibers (asbestosis) or bird proteins (hypersensitivity pneumonitis), or it can occur as clusters in families, so-called familial pulmonary fibrosis (FPF). Indeed, it is emerging that FPF is probably much more common than previously thought, with a recent study identifying a family history of pulmonary fibrosis being associated with a 12-fold increased risk of IPF (1), and in ~25% of asymptomatic family members of patients with IPF there was evidence of subclinical interstitial lung abnormalities (24). Although there are a large number of genes that promote the development of pulmonary fibrosis including common variants in the MUC5B promoter, DSP, and AKAP13 and rare variants in genes related to surfactant production and telomere function (RTEL1, PARN, TERT, and TERC), the proportion of the genetic risk explained by these variant remains small and there is considerable further work required to identify causal variants. For example, the best-described, and most commonly found, rare variants are in a number of genes associated with telomere function, which lead to shortened telomeres, but they are responsible for only ~20% of FPF (34). Furthermore, these variants have also been found in people with IPF, where they also lead to shorter telomeres and are associated with a worse prognosis (14, 41), although the proportion of risk explained in IPF is likely to be smaller than in FPF. Interestingly, males with FPF caused by TERT mutations have a lower age of death than females (13). Short telomeres lead to a process of accelerated aging known as cellular senescence, and indeed cellular senescence is particularly associated with pulmonary fibrosis, raising the prospect that senolytics may be useful therapies in IPF (16, 48, 60). Somewhat worryingly in the context of the global COVID pandemic, a number of studies have demonstrated that virus-induced lung injury leads to worse pulmonary fibrosis in aged mice (7, 40, 57), and understanding the relationship between SARS-CoV-2 infection and ARDS in elderly patients, or those with telomere gene mutations, is clearly going to be important to understand the risk of developing post-COVID pulmonary fibrosis.

**METABOLIC SYNDROME AND IPF**

Metabolic syndrome is the combination of abdominal obesity, insulin resistance, hypertension, and hyperlipidemia (47). Patients with IPF are usually overweight, with an average body...
mass index (BMI) of >28 kg/m² (18, 27), and are more likely to have diabetes and hypertension at diagnosis than matched non-IPF control subjects, leading to an increased risk of cardiovascular disease (11). Metabolic syndrome is associated with increased activity of mammalian target of rapamycin (mTOR) and reduced activity of AMPK (AMPK) (20, 46), and these two key metabolic pathways have been implicated in the pathogenesis of pulmonary fibrosis and, which may afford therapeutic opportunities, mTOR regulates cell growth and proliferation. mTOR forms two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is regulated by multiple signals such as growth factors, amino acids, and cellular energy, activates numerous essential cellular processes including translation and transcription, and inhibits autophagy and has also been implicated in other pathological processes including cancer (39). There is evidence of increased mTOR signaling in IPF both from experimental (37, 61) and genetic (3) studies. Furthermore, inhibitors of mTOR are well tolerated and able to inhibit cellular metabolism in patients with IPF (31). AMPK is a cellular bioenergetic sensor and metabolic regulator (25). Metformin is an AMPK activator, has been shown to inhibit established fibrosis via activation of AMPK (45), and promotes resolution of fibrosis by altering myofibroblast cell fate (29), although observational data from clinical trials in patients with IPF are not supportive of metformin for use in patients with IPF (53). The increased risk of severe COVID-19 in patients with metabolic syndrome is also well described and is leading to policy changes in the United Kingdom. Similarly, inhibitors of mTOR have been identified as a potential novel therapy for COVID-19 (19), and observational studies have identified that metformin is associated with reduced mortality in COVID-19, particularly in women (6, 32). Understanding the interaction between cellular metabolism, respiratory infection, and fibrosis is likely to lead to important insights.

VIRUS-INDUCED PULMONARY FIBROSIS

It is not possible to discuss the etiology of pulmonary fibrosis in 2020 without considering the role of viruses. Early analysis from patients hospitalized with COVID-19 suggests a high rate of lung function abnormalities consistent with pulmonary fibrosis, particularly impaired gas transfer (47%), although this may reflect in part the vasculopathy that is emerging as a key feature of COVID-19. In patients hospitalized with SARS abnormalities in gas transfer were observed in 16% and abnormal chest X-rays were observed in 30%, and 62% of patients had computed tomographic (CT) evidence of pulmonary fibrosis soon after hospital discharge (5, 23). In a follow-up study of 36 patients surviving Middle East respiratory syndrome (MERS) coronavirus infection, 33% had radiographic evidence of pulmonary fibrosis (12). The role of other respiratory viruses in promoting pulmonary fibrosis is less clear and is generally limited to acute exacerbations of IPF and in vivo models (10, 28, 44).

However, there is clear evidence for a role of virus-induced fibrosis in the liver. Hepatitis C, which like the coronaviruses, is a positive-sense single-stranded RNA virus, is a potently fibrogenic virus, leads to over 200 million infected people worldwide, and is a major indication for liver transplantation (49). Furthermore, there are some historical data suggesting a high prevalence of hepatitis C in patients with IPF (4, 35, 59).

More recent data have suggested that viral infections are also associated with an increased risk of IPF; again these were related primarily to chronic rather than acute viral infections (50) and support data implicating herpesviruses as an etiological factor for IPF. The fact that these viruses establish lifelong latency and may reemerge as cell-mediated immunity wanes with aging makes for a compelling hypothesis (38). Whether COVID-19 can lead to progressive pulmonary fibrosis at the current time remains to be determined, but clearly this is an area in urgent need of study to inform the likely risks of long-term post-COVID disease.

CONCLUSIONS

COVID-19 and pulmonary fibrosis are severe diseases characterized by lung injury and repair. In some people, particularly elderly men with metabolic syndrome, there is dysregulated repair that may be due to a genetic predisposition or prolonged environmental exposures to inhaled matter or ingested calorific foods, coupled with shortening telomeres and waning cell-mediated immunity with advancing years. This failing repair may manifest as an overexuberant immune response exacerbating viral injury in COVID-19 or excessive fibroblast proliferation and matrix synthesis in pulmonary fibrosis. The mechanisms driving the failing repair may, however, be linked, and therefore studying these molecular pathways in detail may reveal evidence to support repurposing drugs such as metformin or senolytics such as danazol or trialing compounds inhibiting mTOR or TGF-β signaling and improve outcomes in both conditions.

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AUTHOR CONTRIBUTIONS

G.J. prepared figure; drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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