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COVID-19 and Pulmonary Fibrosis: A Potential Role of the TGF-β pathway

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Abstract

The COVID-19 pandemic spread rapidly worldwide in late 2019. The disease, caused by the new SARS-CoV-2 virus, is primarily a respiratory disease that with poor outcomes in people with aging/comorbidities such as chronic lung disease, diabetes, or cardiovascular disease. The severity of the disease varies from asymptomatic to severe acute respiratory distress that needs special care and mechanical ventilation, which can result in respiratory failure and death. High levels of pro-inflammatory cytokines on account of over-stimulated the intrinsic immune mechanism against the virus leads to the manifestation of lethal clinical signs. It has quickly become apparent that patients with COVID-19 can develop features of interstitial pulmonary fibrosis, which in many patients continues as long as we can follow the patients. Also, histological findings in COVID-19 lung tissue after death show fibrotic lesions with evidence of interstitial fibrosis. Transforming growth factor-beta (TGF-β) is a key inflammatory and pro-fibrotic factor that is released during SARS-CoV-2 infection and it seems that to have a role in pulmonary fibrosis post COVID-19. This mini-review gathers our existing knowledge about the possible role of the pro-fibrotic cytokine pathway TGF-β in post COVID-19 pulmonary fibrosis.

Keywords: SARS-CoV-2; COVID-19; Lung; Pulmonary fibrosis; TGF-β pathway

Abbreviation: COVID-19: Coronavirus Disease-2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ARDS: Acute Respiratory Distress Syndrome; PF: Pulmonary fibrosis; TNF-a: Tumor Necrosis Factor-a; TGF-β: Transforming Growth Factor-β; PDGF: Platelet-Derived Growth Factor; DAD: Diffuse Alveolar Damage

Introduction

The new coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), lead to public health crises worldwide due to lack of specific and effective treatment and also high mortality rate [1]. It appeared in December 2019 and rapidly spread affecting millions of people in a few months, and soon became the biggest pandemic over the last two decades [2]. This pandemic situation has caused significant mortality, particularly in elderly individuals with systemic disorders such as chronic lung disease, cardiovascular or diabetes [1,3]. One of the serious complications of SARS CoV-2 is the lower respiratory tract infections. The progress of COVID-19 infection in lungs, can be divided into three main stages: An early stage of infection, involving virus replication, and relatively mild symptoms, the second stage of pulmonary disease, specified by stimulation of adaptive immunity and the predominance of respiratory disorders as the result of lung injury and hypoxemia, and ultimately in patients who develop the most intensive disease, and finally the third systemic hyper inflammation stage [4].

Some common symptoms of COVID-19 infection generally include fever, dry cough, fatigue abatement and losing of olfactory and taste senses, shortness of breath, persistent fever, loss of appetite, constant pain or pressure in the chest, dysgeusia, acute respiratory distress syndrome (ARDS) with epithelial and endothelial injury [5-7]. The severity of COVID19 infection varies from asymptomatic or mild flu-like symptoms to severe infection, which can quickly lead to respiratory distress, requiring intensive care and mechanical ventilation, and can finally, lead to respiratory failure and death [8,9]. How COVID-19 disturbs the physiology and histology of lungs so fast, has not been understood yet. Bellow we consider the pathology of lung infected by COVID-19 in more detail.

Mechanism of Post COVID Pulmonary Fibrosis

Radiology findings revel that, most patients with SARS-COV-2 confront bilateral ground-glass opacities with or without consolidation with more involvement in the lower lobes [10]. However, it should be borne in mind that long-term lung dysfunction may result from clearance of the virus and in particular interstitial fibrotic disease of the lung. Pulmonary fibrosis can be idiopathic or caused by chronic inflammation [11]. Pulmonary fibrosis (PF) is an interstitial lung disease, specified by progressive scarring of lung tissue. It has been known that lung inflammation causes proliferation of fibroblasts, and deposition of extracellular matrix proteins and demolition of the alveolar structure. These pathologic changes result in poor ventilation and ultimately respiratory failure [12].

Studies showed that various cytokines like tumor necrosis factor-a (TNF-a), transforming growth factor- β1 (TGF-β), and platelet-derived growth factor (PDGF) are involved in the progression of pulmonary fibrosis. Particularly transforming growth factor-beta1 (TGF- β1) seems to be a main pro-inflammatory cytokine that stimulates fibroblast proliferation, transformation to a contractile myofibroblast phenotype, and induces the production and deposition of the extracellular matrix proteins [12]. In the early pathogenesis of PF, the alveolar epithelium cells (which comprised of type I: ATI and type II: ATII) are the early core sites of primary damage. It is assumed that the loss of ATII cells, can initiate fibrogenesis, because their physiological roles are very important [13-15].

In response to injury, the alveolar epithelium releases a set of inflammatory cytokines and regenerative mediators, particularly, TGF- β and implicates in PF pathogenesis [16]. Transforming growth factor-beta1 (TGF- β1) released by damaged alveolar epithelium affects fibroblast and activates them to initiate pro-fibrotic responses and contributes to the progression and development of pulmonary fibrosis [17]. Although the reason for rapid increase in mortality from SARS-CoV-2 infection, has not understood yet, there are evidence showing a relationship between the rate of fibrotic change following severe acute lung injury and mortality [18].

Histological findings in lung tissue infected with COVID-19 after death indicate the presence of diffuse alveolar damage (DAD), thickening of alveolar septa, the proliferation of fibroblasts, and evidence of fibrosis (2). Generally, three main histological patterns are as follows: (1) reactive epithelial changes and diffuse alveolar damage (DAD). (ii) Vessels with microvascular damage, (micro) thrombi, fibrinous and organizing pneumonia, and (iii) fibrotic with evidence of interstitial fibrosis [19].

The Role of TGF -β In the Pathology of SARS -CoV-2 Infection

There is growing evidence showing that many patients with COVID-19 have fibrotic complications and changes in their lung function that indicate restrictive lung disease [18,20-23]. Following the entry of the virus into the host, activation of the intrinsic immune mechanism occurs along with the synthesis and secretion of inflammatory mediators [24]. High levels of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-18, IL-33, IFNα, IFNγ, TNFα, TGFβ and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, are related with pulmonary inflammation and ARDS in patients infected by SARS COVID-19 infections [12,25]. Finally, severe inflammation and the "cytokine storm" suggest participation in the pathogenesis of COVID-19 [26]. One of the important growth factors released during SARS-CoV-2 infection is transforming growth factor-beta (TGF-β), which as well as plays an important role in pulmonary fibrosis [27].

It has been assumed that immune cells such as neutrophils or damaged cells by SARS-CoV-2 may be the source of TGF-β secretion [27-29]. Researchers have also recently shown that both mRNA and protein of TGF-β together with its signaling pathway are up regulated during SARS-CoV-2 infection (which comprise nucleocapsid (N) protein and spike (S) protein) [30-32], It is assumed that SARS-CoV-2 up regulates TGF-β by down regulating the angiotensin-converting enzyme receptor 2(ACE2) through the interaction of the spike protein with ACE2. Consequently down-regulation of ACE2, enhances the level of angiotensin-II (ANG-II) which leads in increased intracellular TGF-β signaling pathway activity [27,33-36]. Moreover, the N protein of SARS CoV-2 leads to increase in the signaling pathway activity of TGF-β intracellular by interaction with SMAD3 [37,38]. However, more research is needed to enhance understanding of the relationship between SARS-CoV-2 and TGF-β.

The Role of TGF -β in the Post COVID Pulmonary Fibrosis

Studies showed that damage to alveolar epithelial cells, causes the infiltration of fibroblasts, then inflammatory cells release pro-fibrotic mediators like TGFβ [39]. TGFβ leads to matrix synthesis and accumulation and regulate lung injury and fibrosis [16,28]. For example, over-expression of TGF-β has been reported in animal studies to lead to progressive pulmonary fibrosis [40]. The researchers showed that increased TGF-β may suppress type I interferon responses by alveolar macrophages, thereby increasing the likelihood of persistent viral infection [41]. Although studies show that fibrosis persists for months after the infection is gone. Whether these changes occur merely as a transient response to a viral infection or maintain over time, needs more investigations [21,42,43]. Also, these findings may propose the role of pro-fibrotic cytokine TGF-β in COVID-19-induced pulmonary fibrosis.

TGF-β Signaling Pathway

As we mentioned above, the transforming Growth Factor-β (TGFβ) family of peptides is a regulator of the fibrotic response that plays a central role in the maladaptive remodeling of the heart after injury [44,45]. TGF-β is known as a powerful activator

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of fibroblasts that can induce myofibroblast activation, collagen deposition and wound contraction [46]. The canonical pathway of TGF-β1 signaling involves the phosphorylation of Smad2/3, which subsequently binds Smad4 and translocate to the nucleus. Phosphorylation of SMAD2 and SMAD3 by TGF-b1 induces nuclear transcription, and starts various expression of genes, which includes fibrosis-associated signals [47]. On the other hand, the SMAD2/3 signaling pathway is essential for fibroblast to myofibroblast differentiation induced by TGF-β1 [47]. Also, in animal study showed that cardiac fibrosis is associated with increase in expression of TGF-β1 and Smad2/3 [45]. However, it seems that further research is required to better understand the role of TGF-β in SARS-CoV-2 infection.

Conclusion

The new coronavirus-induced disease led to a pandemic that spreads quickly and has caused many infections and deaths worldwide. Many patients with COVID-19 suffer from lung injury such as pulmonary fibrosis. Although COVID-19 infection can cause pulmonary fibrosis, the clear link between COVID-19 infection and pulmonary fibrosis is not yet clear. There is growing evidence that fibrotic changes and interstitial lung abnormalities may be caused by COVID-19 infection, but how these changes progress and the persistence or progression of fibrosis is unknown. We hypothesize that such fibrotic changes may occur due to an intrinsic immune mechanism, along with the synthesis and secretion of inflammatory mediators such as TGF-β. However, immediate research is needed to identify the cellular and molecular mechanisms that lead to fibrotic changes following SARS-CoV-2 infection.

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