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Reviews

POSSIBILITIES OF USING MEDICINES AND BIOLOGICALLY ACTIVE SUBSTANCES AS CORRECTIVES FOR THE FORMATION OF PULMONARY FIBROSIS DURING SARS-COV-2 INFECTION AND IN THE POST-COVID PERIOD

Shulgau Z.T.*, Kamyshanskiy Y.K., Gulyayev A.Y.

Republican State Enterprise "National Center for Biotechnology", Kurgalzhynskoye road 13/5, Nur-Sultan, 010000, Kazakhstan
**shulgau@biocenter.kz*

ABSTRACT

A systematic review of the literature on the pathophysiology of fibrosis in interstitial lung diseases was carried out. The results of clinical studies of the effectiveness of antifibrotic drugs are summarized. Particular attention is paid to the development of fibrosis associated with Covid-19 infection. The results of the study of the most promising drugs that prevent the development of fibrosis in this pathology are described. The prospect of developing drug therapy based on plant polyphenols is emphasized.

Key words: Pulmonary fibrosis, pathogenesis of pulmonary fibrosis, antifibrotic drugs

INTRODUCTION

Pulmonary fibrosis (PF) can occur as one of the most severe and common consequences of COVID-19 [1], accompanied by distortion of the histoarchitectonics of lung tissue, potential lung dysfunction and a decrease in quality of life [2]. The prevalence of fibrotic lung changes after COVID-19 according to various studies varies from 25.5% to 84.15% [1,3-6]. Meanwhile, the functional significance of the damages, their reversibility and prognosis remain uncertain.

In support of the hypothesis that after infection with SARS-CoV-2, some patients may develop PF, firstly, the prevalence of acute respiratory distress syndrome in severe COVID-19 advocates. The pathogenesis of severe acute respiratory distress syndrome (ARDS) in COVID-19 includes typical manifestations of pulmonary fibrosis (PF) [7]. At the microscopic level, the predominant histopathological pattern is diffuse alveolar injury [8]: interstitial/alveolar edema [9-12], inflammatory lymphocytic infiltrate [13-16] and hyaline membranes, as well as histopathological signs of organizing pneumonia with intraalveolar exudate [17,18], squamous metaplasia [19,20], microthrombs [21,22], hyperplasia of type II pneumocytes [23,24], thickening of the interalveolar septa [25,26] and atypical enlarged multinucleated and syncytial pneumocytes [27], which are signs of a vascular pattern with microvascular lesions, blood clots and acute fibrinous and organizing pneumonia and a fibrous pattern with signs of interstitial fibrosis. PF in these cases may develop after acute injury, due to the destruction of the normal structure of the lungs, the persistence of fibroblasts and myofibroblasts, unsuccessful reconstruction of the damaged alveolar epithelium and excessive deposition of collagen and other components of the extracellular matrix [28]. Additional factors that increase the risk of developing Post-Covid interstitial lung disease are mechanical stretching of alveolocytes during artificial ventilation of the lungs which causes a fibrous reaction [29,30].

Secondly, given the similarity of SARS-CoV-2 to both SARS and MERS, there is a possibility of similar long-term pulmonary complications after COVID-19 [31-36]. The MERS research showed that fibrous changes were observed on radiographs in one third of patients after discharge from the hospital [35]. Das et al. [37] revealed ground-glass opacity of on radiographs 1 year after acute infection in 66% of patients. SARS-CoV studies have shown that from 27.8% to 62% of patients infected with SARS-CoV demonstrate decreased lung function and increased fibrosis [34,38-40]. Data from a longer observation after 15 years showed that about 9% of the participant of research had fibrotic changes after infection, and although this percentage decreased slightly to 4.6% within one year, it remained stable until a 15-year observation period in 2018 [41]. In addition, PF resolution was found in some patients, which indicates that PF caused by SARS-CoV infection may be reversible, but recovery mechanisms require additional research [42,43].

Thirdly, a number of studies report that some viruses are associated with PF and remain a risk factor for the development of PF for a long time after infection [44-51] acting as suspected triggers of autoimmunity, which theoretically increases the likelihood of developing pulmonary fibrosis in asymptomatic forms and mild infection. According to some authors, delayed lung damage after infection with SARS-CoV-2 may be due to an autoimmune response to ACE2 [52]. In accordance with another hypothesis [53], hypoxia can induce the expression of anti-stress proteins having various similar antigens, which may cause cross-immunological reactivity between chaperones and viral proteins and lead to the formation of antibodies that damage pneumocytes and endotheliocytes with the development of microthrombosis, disseminated intravascular coagulation and multiple organ failure [54,55]. These data allow to suggest the presence of delayed interstitial pneumonia and PF in the long-term period.

Currently, the understanding of the pathogenetic mechanisms of PF after COVID is developing. The factors mediating the profibrotic response after coronavirus infection are not known, but suggest that the features of the innate immune response [56], the profile of gene expression in myeloid populations [57], hyperactivation of alternatively activated macrophages [58], as well as the expression of proinflammatory and profibrotic factors during the acute period of infection [59,60] are important. With SARS-CoV-2, the etiology of PF should also take into account a relatively specific set of growth factors and cytokines, including monocyte chemoattractant protein-1 (MCP-1), transforming growth factor β1 (TGF-β1), tumor necrosis factor α (TNF-α), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), interleukin-1b (IL-1b) and interleukin-6 (IL-6), which are overexpressed and released by cells [61,62].

An additional mechanism may be oxidative stress associated with excessive formation of reactive oxygen species (ROS). [63,64]. Moreover, tyrosine kinase signaling mediated by fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) is also crucial in the development of pulmonary fibrosis. Studies determining the pathogenesis of idiopathic pulmonary fibrosis (IPF) have shown that overexpression of FGF and PDGF increases the proliferation of pulmonary fibroblasts. In addition, FGF enhances the profibrotic effects of TGF-β1 [62].

Dysregulation of the release of matrix metalloproteinases, which causes damage to the epithelium and endothelium with degradation of the extracellular matrix [65] and uncontrolled fibroproliferation, are among the most important factors of the inflammatory phase of ARDS in SARS-CoV-2 [66]. TGF-β1 regulates fibrosis [67] and, together with VEGF, IL-6 and TNF-α, participates in the progression of fibrosis [68]. Overexpression of TGFβ *in vivo* stimulates fibroblast proliferation, myofibroblast transdifferentiation, and progressive lung fibrosis [69]. This process does not occur in all patients and is nonspecific exactly for SARS-CoV-2 [28].

Treatment of pulmonary fibrosis after COVID-19 infection remains an unexplored problem due to the lack of results of clinical trials, the most of which are currently either only planned or in the initial stages of implementation. These circumstances force us to take into account the probable risk of developing chronic pulmonary fibrosis over time in the covid and post-covid period, so we strive to revise current knowledge about this phenomenon and methods of its correction.

Pathogenetic therapy of COVID-19 as a factor of correction of pulmonary fibrosis

We consider it possible to make a reservation right away that attempts to prevent pulmonary fibrosis through the use of antiviral drugs, as the outcome of COVID-19, do not yet give due optimism. Viral protease inhibitors: lopinavir/ritonavir, with RNA polymerase inhibitors: favipiravir and remdesivir, are antiviral agents that are currently being used in many clinical trials in an attempt to find an effective therapy against SARS-CoV-2 [70-72]. Antimalarial drugs chloroquine/hydroxychloroquine have been used in many clinical trials due to antiviral properties; however, there have been no reports confirming a clear benefit in preventing fibrosis [73].

Among other drugs with antiviral and immunomodulatory properties, are usually called nitazoxanide and ivermectin (both have demonstrated activity against SARS-CoV-2), their effectiveness in the treatment of COVID-19 is being investigated [74-77].

Indeed, a number of early antifibrotic studies were focused on key antiviral proteins, such as IFN-β and IFN-γ [78]. Subsequent studies have shown that exogenously administered as well as endogenously produced interferon can cause pulmonary vasculopathy [79,80], which may be important in the development of severe COVID-19 disease form. Indeed, circulating concentrations of IFN-γ are elevated in patients with severe COVID-19 form [81].

From the standpoint of pathophysiology, the main goal of antifibrotic therapy in COVID-19 can be considered the TGF-β pathway. It is encouraging, given the role of TGF-β in immunity, that suppression of epithelial integrins and galectins does not seem to increase the risk of viral infection, which has been shown on several animal models [67]. A number of drugs are in development that target various molecules in this pathway, including inactivators of integrin avß6 (BG00011 [Biogen, Cambridge, Massachusetts, USA]; PLN-74809 [Pliant Therapeutics, San Francisco, California, USA]) and galectins (TD139 [Galectobiotech, Copenhagen, Denmark]) [51,82]. These substances can be considered particularly interesting candidates, since SARS-CoV-2 contains the integrin-binding domain Arg-Gly-Asp and a number of coronaviruses contain an N-terminal galectin fold [83], which increases the likelihood that inhibition of integrins or galectins may be useful in the treatment of COVID-19 and prevention of fibrosis. In addition, the substance PRM-151 (Roche, Basel, Switzerland), an analog of SAP (also known as PTX2 – mouse recombinant protein), part of the pentraxin family of proteins, showed promising results in a phase 2 trial for IPF [84]. Pentraxins are known to be among the acute phase proteins that have a key role in inflammation and immunity [85]. Recombinant SAP injection has been shown to reduce inflammation 7 days after bleomycin-induced lung injury in mice [86], this selective JNK1 inhibitor prevents fibrosis on some experimental animal models [87]. However, experimental data confirming that the use of these substances in viral lung damage prevents fibrosis are not yet available.

Vicor Pharma company has presented the results of clinical trials of C21 (AT2R agonist) during IPF and now this drug is approved for a phase 2 study in COVID-19 (EudraCT 2017-004923-63). The role of the renin-angiotensin system in SARS-CoV-2 is well documented, but it is not yet clear how to use it for search of new drugs [88]. The role of angiotensin receptor inhibitors in COVID-19 is controversial [89].

Since the role of IL-1 in the pathogenesis of PF is well described [90], there is an opinion that inhibition of IL-1 can also prevent the development of post-COVID-19 fibrosis. The role of anti-IL-6 strategies is less known. IL-6 is considered to be a profibrotic molecule [91-93]. An experimental study of pulmonary fibrosis on a bleomycin model shows that inhibition of IL-6 at an early stage of lung damage promotes fibrosis, and inhibition at later stages of injury at the beginning of the fibrous phase can prevent fibrosis [94].

Since the cytokine storm due to hyperinflammation is the main factor of lung damage in SARS-CoV-2 infection, the use of immunosuppressants is widely recommended for the treatment of COVID-19 and the prevention of fibrosis [95]. Immunosuppressive agents currently under consideration include an IL-1 receptor blocker (Anakinra, Swedish Orphan Biovitrum AB)), which has demonstrated improved survival in cytokine storm due to sepsis, and an IL-6 receptor blocker (tocilizumab) [96,97]. Despite the widespread use of corticosteroids, there is little data confirming their clinical benefit [98].

Possibilities of using mesenchymal stem cells to reduce the risk of pulmonary fibrosis formation

Attempts are being done to use mesenchymal stem cells (MSCs) in the treatment of SARS-CoV-2 infection, while also indicating that it is possible to reduce the risk of pulmonary fibrosis formation as a result of the use of MSCs [99].

It has been suggested that MSCs can improve acute lung injury and control the cell-mediated inflammatory response

stimulated by coronavirus [100]. Additionally, MSCs can change the microenvironment of lung cells by reducing the level of profibrogenic factors and can reduce tissue damage by preventing cell death [101]. Of course, all these immunomodulatory characteristics provide a significant potential of MSCs in clinical therapy. Consequently, MSCs can have a positive effect on the severe stage of COVID-19 pathology and generate several immune interactions with released cytokines and intercellular contacts. The above factors are favorable for the treatment of ARDS caused by COVID-19.

The safety of MSCs treatment in patients with ARDS has been demonstrated in a number of researches [102-104]. It is reported that additional MSCs therapy in COVID-19 contributes to the relief of breath shortness and is characterized by a shorter recovery period [105-108]. CT scans of the lungs also showed a marked decrease in fibrous pulmonary lesions, including a decrease in pathological foci of the ground-glass opacities and seals [109,110]. In a double-blind placebo-controlled study, the administration of MSCs significantly reduced the volume of the solid component for 28 days in patients with severe COVID-19 [110]. During follow-up for one year, patients treated with MSCs experienced a decrease in the volume of the solid component of the lesion and improved lung function, indicating that MSCs therapy may have long-term benefits [111].

Hypothetically, MSCs can improve acute lung injury and control the cell-mediated inflammatory response stimulated by the coronavirus. MSCs can settle in the vascular bed of the lungs after injection, secrete anti-inflammatory mediators and reduce the cytokine storm caused by a viral infection. Further, MSCs can induce the secretion of angiopoietin-1 and epidermal growth factor (EGF), other growth factors, including insulin-like, which are important for the restoration of alveolar-capillary barriers damaged by COVID-19 and that is what matters as an obstacle to the formation of pulmonary fibrosis [112]. However, this effect manifests itself contradictory and depends on external stimulation and the state of the MSCs. Thus, opposite results were obtained in an experiment on a mouse model of bleomycin–induced pulmonary fibrosis – to protect the lung epithelium from apoptosis in mice and facilitate the restoration of vascular endothelium [113,114] to the opposite effect, - increased fibrosis [115]. On ClinicalTrials.gov more than 90 clinical trials have been registered in which MSCs are used to treat COVID-19, more than half of these trials are in phase I/II or phase II. It is too early to draw final conclusions from the preliminary clinical results [116], but there is a chance that intravenous MSCs transplantation may represent a safe and effective treatment of patients with COVID-19 pneumonia, especially critical ones. It is hoped that MSCs can suppress excessive activation of the immune system and will contribute to the prevention of pulmonary fibrosis [117].

Possibilities of searching for correctors of pulmonary fibrosis among repurposed drugs

Given the presence of some common pathophysiological mechanisms between IPF and PF as a result of COVID-19 infection, the attention of researchers is drawn to drugs certified for IPF therapy.

A few years before the present pandemic, two drugs, nintedanib and pirfenidone, showed promising results in clinical trials in slowing the pulmonary function decline during IPF [118,119]. Nintedanib is a tyrosine kinase inhibitor active against growth factor receptors with intrinsic tyrosine kinase activity, such as EGFR, VEGFR and PDGFR [120]. Pirfenidone inhibits TGF-β-induced fibronectin synthesis and can reduce lung damage caused by cytokine storms after infection with SARS-COV-2 due to a significant decrease in serum and lung IL-6 levels [121-123].

However, it should be emphasized that neither of these two drugs demonstrated significant improvement in symptoms or improvement in long-term survival in IPF [124].

In general, the emerging individual results of the use of drugs intended for the treatment of IPF do not yet allow us to assess positively the prospects of such therapy [125].

During 2020-2021, the following clinical trials of other drugs previously intended for the treatment of IPF according to new indications for the treatment of PF in SARS-CoV-2 are continuing: Nintedanib NCT04338802 phase II; Pirfenidone NCT04282902 phase III; Tetrandrine NCT04308317 phase IV; collections of Chinese herbs - FuzhengHuayu Tablet NCT04279197 and Anluohuaxian NCT04334265 - Phase II [28].

It is known that chronic obstructive pulmonary disease (COPD) is a slow-developing lung disease, for which the outcome in pulmonary fibrosis with respiratory failure and pulmonary heart failure is typical, therefore, drugs for the treatment of COPD can also be considered for reprofiling in SARS-CoV-2 [126]. A group of phosphodiesterase (PDE) inhibitor drugs that regulate the activity of inflammatory cells and the release of inflammatory factors attract attention. It is assumed that PDE inhibitors may be an important pharmacological target for the treatment of postcovid fibrosis [127-130]. Recently, it was PDE inhibitors that were identified as substances capable of blocking infiltration by neutrophils, monocytes and lymphocytes of the lung epithelium [131]. It is assumed that the ability of roflumilast to inhibit bleomycin-induced pulmonary fibrosis in rats and reduce pulmonary vascular remodeling can also be used in PF caused by SARS-CoV-2 [132,133]. The possibility of using pentoxifylline to reduce PF by lowering the expression of platelet activation factor (PAI)-1 and fibronectin [134] or by blocking TGF-β1 and reducing the deposition of type I collagen [135] is being investigated (NCT04433988).

In addition, other PDE inhibitors are of significant interest as a means of inhibiting PF. Hypothetically, other selective phosphodiesterase inhibitors, in particular, type 3 phosphodiesterase inhibitor (PDE-3) cilostazol, which, being an antiplatelet and vasodilator drug, has a number of pleiotropic effects, such as anti-apoptotic, anti-inflammatory, antioxidant and cardioprotective effects, can be attributed to the number of candidate compounds for testing on PF models [136].

It has been established that cilostazol can also inhibit adenosine uptake, which increases intracellular cAMP levels, and in the lungs, increased cAMP contributes to antifibrotic, vasodilating, antiproliferative effects, as well as a decrease in the inflammatory process [137]. Since cilostazol exhibits important anti-inflammatory, antiplatelet, immunomodulatory, antioxidant and cardioprotective properties due to inhibition of PDE-3, we really believe that it can play an important role.

in the treatment of COVID-19, especially in the fight against cytokine storm and consequences in the form of fibrosis [138].

The ability of another group of drugs, dipeptidyl peptidase–4 (DPP4) inhibitors, to reduce the production of proinflammatory cytokines against the background of acute respiratory distress syndrome clinic in SARS-CoV-2 infected patients [139] allows some researchers to assume the likelihood of reducing the risk of lung fibrosis after the use of DPP4 drugs [140], although there is no direct evidence yet received. At the same time, of course, careful experimental studies are needed, because widely used inhibitors (for example, sitagliptin, alogliptin, vildagliptin, saxagliptin, linagliptin) bind to a strictly defined DPP4 catalytic site, while SARS-CoV-2 interacts with another DPP4 site and their effects do not directly overlap with DPP4 inhibitors [141].

Possible correctors of pulmonary fibrosis among biologically active compounds affecting the mTOR pathway, autophagy, mitophagy

Interesting data are emerging regarding the relationship between the pathogenesis of SARS-CoV-2 and the mTOR pathway. In particular, it was found [142] that suppression of the expression of mTOR, mitochondrial ribosomes, mitochondrial complex I and lysosome acidification genes is simultaneously observed in infected cell lines. In addition, the same authors found, as well as [143], that SARS-CoV-2 infection interferes with autophagic flow by activating GSK3B in lung cell lines or suppressing autophagy genes, SNAP29 and lysosome acidification genes, which contributes to increased virus replication. Consequently, drugs aimed at acidification of lysosomes or autophagic flow can be tested as an intervention strategy.

Of course, further research is needed on the complex relationship between viral infections, in particular SARS-CoV-2, and autophagy. The information found in the literature confirms the plausibility of the manifestation of therapeutic efficacy when using autophagy as a target for suppressing hyperinflammation and fibrosis, but in general, the situation with targeting autophagy seems inaccurate. It is known [144] that autophagy activators can help a cell absorb an incoming virus or accelerate the creation of virus replication complexes and accelerate the development of the disease. It is likely that autophagy inhibitors can work in the later stages of infection to weaken the production of the virus, but this will depend on whether autophagy is active at the moment or the constituent components have been captured and effectively disabled.

However, it should be emphasized that at the third and critical stage of COVID-19 (characterized by an uncontrolled inflammatory process and determining the actual transition to fibrosis of lung tissue), the administration of autophagy activators may be useful. It is known that some drugs, for example, metformin and everolimus, act as inducers of autophagy, although their mechanisms are not yet clear. Two recent network analyses of protein-protein interactions have shown that mTOR can be an anti-SARS-CoV-2 target, and rapamycin can be repurposed for this indication [145,146]. Simvastatin is another drug known to enhance autophagy via the mTOR pathway [147]. Simvastatin has also been reported to alleviate airway inflammation on an asthma model in mice [148]. Another autophagy modulator is niclosamide, which regulates autophagy by acting on the autophagy regulator Beclin1 via the SKP2 E3 ligase. In MERS-CoV infection, a decrease in Beclin1 leads to blocking the fusion of autophagosomes and lysosomes, and, consequently, the virus protects itself in the host body [149]. Inhibition of SKP2 by niclosamide weakens Beclin1, allowing the fusion of autophagosomes and lysosomes and the resumption of autophagy to reduce the production of MERS-CoV. In addition, niclosamide (an FDA-approved drug for the treatment of tapeworm infection) and valinomycin (a natural antibiotic) also target SARS-CoV in cell cultures [150].

Moreover, resveratrol attracts attention as an inducer of autophagy, also this polyphenol has well-known antiviral and anti-inflammatory activity, and the latter, apparently, is directly related to autophagy [151]. To date, there are also a considerable number of compounds from plant polyphenols similar to resveratrol (quercetin, kaempferol, epigallocatechin, dihydroquercetin, curcumin, grape polyphenol complex, blueberry polyphenol complex) that actively interact with autophagy [152-155].

We agree with the opinion [156] that today autophagy, as a target of candidate compounds for the pathogenetic therapy of COVID-19 and the reduction of the risk of pulmonary fibrosis, has not yet received due attention. We assume that further research is needed to improve knowledge about such mechanisms, as well as clinical trials of drugs aimed at autophagy using mono- or combination therapy with the use of inhibitors or activators of certain autophagy pathways.

The question of the role of mitochondrial autophagy as a target for potential antifibrotic drugs deserves special attention. Selective mitochondrial autophagy (mitophagy) is involved in controlling the number of mitochondria in the cell by removing damaged organelles, which helps the cell to survive and respond to aggression, including coronavirus infections [157].

Thus, therapy with drugs that activate mitochondrial and general autophagy could have a protective effect, decreasing susceptibility to the virus and reducing the effects associated with overproduction of free radicals, excessive activation of the inflammatory response and cytokine storm. In this sense, we agree with the opinion of D. Michalikova et al. [158,159] and also point to compounds that stimulate autophagy, in particular, that cause mitochondrial autophagy, as candidate compounds in the therapy of COVID-19 and its consequences.

The so-called senolytic activity of the body is also associated with the processes of autophagy. There is reason to believe that elderly patients with COVID-19 are more likely to accumulate a higher than usual level of cellular aging indicators (SASP - senescence-associated secretory phenotype) for three reasons: (a) the number of aging cells is already increased at the time of infection; (b) old cells are unable to repair damage associated with the development of the infectious process in the presence of SARS-CoV2; (c) old tissues are less able to destroy aging cells due to the perversion of immune functions caused by SARS-CoV2 [160]. As a result, a decrease in senolytic activity may become a factor aggravating the pathogenesis of COVID-19. Some senolytic drugs have recently undergone preclinical and clinical studies, for example, a combination of the protein kinase inhibitor dasatinib with the flavonoid quercetin [161], and quercetin itself is being tested as a senolytic drug for SARS-CoV2

[162]. Thus, biologically active compounds with the presence of senolytic activity can also be used as candidate compounds in the search for means of correcting pulmonary fibrosis in COVID-19.

Possibilities of searching for correctors of pulmonary fibrosis among phytochemical substances

Phytochemical substances should probably be considered as candidate compounds for the containment of pulmonary fibrosis.

Considering a total of 150 natural compounds as potential candidates for the development of new anti-COVID-19 drugs [163], several natural compounds have been identified that require further study. The authors point to at least 24 natural plant compounds with potential effects against COVID-19. This list includes chalcones, flavonoids, phenolic acids, polyphenols, anthraquinones, diarylheptanoid and biphenylpropanoid. Among them, the natural flavonoid quercetin is indicated as a leading candidate with its ability to inhibit the interaction of SARS-CoV S protein and ACE2, viral protease and helicase [164,165], but RAAS (renin-angiotensin-aldosterone system) is also indicated as an additional mechanism. A strategy involving RAAS regulates blood pressure, inflammation, and the formation of pulmonary fibrosis (by converting angiotensin II into lung protective angiotensin-1e7) [166]. Other researchers, without identifying specific substances, claim the possibility of a therapeutic potential for SARS-CoV2 infection in the class of polyphenols in general [167].

Another review [152], considering polyphenols, also identifies quercetin and kaempferol as the most promising correctors of pulmonary fibrosis in COVID-19. It has been shown that both quercetin and kaempferol, two natural flavonoids, have an antifibrotic effect on a model of severe progressive pulmonary fibrosis by induction of autophagy [168-170].

Another phytochemical compound from fungi of the Cordyceps genus – cordycepin, on COPD models, improves morphological changes in tissues, preventing the development of subepithelial fibrosis [171]. Decrease in accumulation of macrophages, neutrophils and lymphocytes in bronchoalveolar fluid, suppression of inflammatory cytokines IL-1β and IL-18, TNF-α, IL-8, TGF-β1, cordycepin reproduces *in vitro* and *in vivo* on models of pulmonary inflammation and pulmonary fibrosis of mice, and in culture of macrophages of human origin [172,173].

Of course, publications concerning the autophagy inducer resveratrol attract attention. It is this polyphenol that has a well-described antiviral and anti-inflammatory activity, and the latter, apparently, is also directly related to autophagy [174]. To date, there are also a considerable number of compounds from plant polyphenols similar to resveratrol (quercetin, kaempferol, epigallocatechin, dihydroquercetin, curcumin, grape polyphenol complex, blueberry polyphenol complex) that actively interact with autophagy [152-155].

In general, according to the numerous available data, polyphenols are endowed with versatile beneficial properties. Antiviral, antioxidant, anti-inflammatory, antidiabetic, antithrombotic and prebiotic effects of polyphenols can be used to combat COVID-19. At the very least, their effectiveness should be tested, given their ability to modulate various molecular, metabolic, and clinical targets of SARS-CoV-2. A thorough study will allow to determine whether they can act synergistically with existing medications against viral infection and related complications. Of particular interest may be the probability of the implementation of polyphenolic antifibrotic effects against the background of the course of SARS-CoV-2, assumed by many researchers, but not clearly proven [175-178].

CONCLUSION

The burden of fibrotic lung diseases after SARS-CoV-2 is likely to be high, given both the scale of the pandemic and the severity of fibrotic lung disease.

The study of specific pathogenetic drugs with SARS-CoV-2 for antifibrotic effects during COVID-19 and during the convalescence period can certainly be considered a priority.

When selecting candidate compounds for testing as potential antifibrotic strategies, the use of drugs previously licensed for antifibrotic therapy in IPF, COPD, viral pneumonia, and repurposing of PDE inhibitors or DPP4 inhibitors is justified.

New antifibrotic strategies may include correctors on the mTOR pathway, autophagy and mitophagy modifiers, a wide range of natural polyphenol compounds, and senolytic agents.

The COVID-19 pandemic combines huge economic, social and health problems. In this context, we considered that it is important to try to predict and prepare for these challenges, in particular considering pulmonary fibrosis syndrome as clearly defined and fairly well characterized.

Ultimately, we hope that the observations highlighted in this review will help focus on more intensive studies of antifibrotic methods of treating severe pneumonia in COVID-19 and preventing the formation of fibrosis in the post-covid period.

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ВОЗМОЖНОСТИ ИСПОЛЬЗОВАНИЯ ЛЕКАРСТВЕННЫХ СРЕДСТВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СУБСТАНЦИЙ В КАЧЕСТВЕ КОРРЕКТОРОВ ФОРМИРОВАНИЯ ЛЕГОЧНОГО ФИБРОЗА ПРИ ИНФИЦИРОВАНИИ SARS-COV-2 И В ПОСТ-КОВИДНЫЙ ПЕРИОД

Шульгау З.Т.*, Камышанский Е.К., Гуляев А.Е.

РГП «Национальный центр биотехнологии», шоссе Коргалжын 13/5, г. Нур-Султан, 010000, Казахстан
**shulgau@biocenter.kz*

АБСТРАКТ

Проведен систематический обзор литературы по патофизиологии фиброза при интерстициальных заболеваниях лёгких. Обобщены результаты клинических исследований эффективности антифибротических лекарственных средств. Особое внимание уделено рассмотрению проблемы развития фиброза, сопутствующего инфекции Covid-19. Описываются результаты исследования наиболее перспективных препаратов препятствующих развитию фиброза при данной патологии. Подчеркивается перспектива разработки медикаментозной терапии на основе растительных полифенолов.

Ключевые слова: Фиброз легких, патогенез фиброза легких, антифибротические лекарственные средства

SARS-COV-2 ИНФЕКЦИЯСЫ КЕЗІНДЕ ЖӘНЕ КОВИДТЕН КЕЙІНГІ КЕЗЕҢДЕ ӨКПЕ ФИБРОЗЫН ТҮЗЕТІН ТҮЗЕТКІШТЕР РЕТІНДЕ ДӘРІЛІК ЗАТТАР МЕН БИОЛОГИЯЛЫҚ БЕЛСЕНДІ СУБСТАНЦИЯЛАРДЫ ПАЙДАЛАНУ МҮМКІНДІГІ

Шульгау З.Т.*, Камышанский Е.К., Гуляев А.Е.

«Ұлттық Биотехнология Орталығы» РМК, Қорғалжын шоссе 13/5, Нұр-сұлтан қ., 010000, Қазақстан
**shulgau@biocenter.kz*

ТҮЙІН

Өкпенің интерстициалды аурулары кезіндегі фиброздың патофизиологиясы бойынша зерттеулерге жүйелі шолу жасалды. Антифибротикалық дәрілік препараттардың тиімділігіне байланысты жүргізілген клиникалық зерттеулердің нәтижелері жинақталды. Ковид-19 инфекциясымен байланысты фиброздың дамуына ерекше назар аударылды. Бұл патологияда фиброздың дамуына жол бермейтін ең перспективті препараттардың зерттеу нәтижелері сипатталады. Өсімдік полифенолдарына негізделген дәрілік терапияны дамыту перспективасы ерекше атап өтілді.

Негізгі сөздер: Өкпе фиброзы, өкпе фиброзының патогенезі, антифибротикалық дәрәләк препараттар