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# Роль трансформирующего фактора роста β в патогенезе фиброза легкого при COVID-19, постковидном синдроме, онкологических и хронических воспалительных заболеваний легких

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***АННОТАЦИЯ***

***Введение.*** Персистирующий постковидный синдром — это стойкие физические, медицинские и когнитивные последствия коронавирусной болезни 2019 г. (англ.: *Coronavirus Disease 2019*, COVID-19), включая стойкую иммуносупрессию, фиброз легких, сердца и сосудов, которые приводят к увеличению летальности и ухудшению качества жизни пациентов.

***Цель.*** Провести анализ завершенных зарубежных и отечественных исследований о патофизиологии трансформирующего фактора роста-β (англ.: *Transforming Growth Factor* β, TGF-β) в условиях COVID-19, постковидного синдрома, онкологических и хронических воспалительных заболеваний легких.

Тучные клетки являются одним из основных продуцентов воспалительных цитокинов при COVID-19, их стимуляция приводит к высвобождению многих провоспалительных цитокинов, таких как интерлейкин 1β, фактор некроза опухоли α, интерлейкин 6, в т. ч. TGF-β. Основой патогенеза постковидного синдрома является сверхэкспрессия TGF-β, приводящая к длительному состоянию иммуносупрессии и фиброзу. TGF-β действует как супрессор опухоли, ингибируя пролиферацию и индуцируя апоптоз на ранних стадиях онкогенеза; играет важную роль в большинстве клеточных биологических процессов, приводящих к ремоделированию структур дыхательных путей; участвует в изменениях эпителия, субэпителиальном фиброзе, ремоделировании гладкой мускулатуры дыхательных путей и микрососудистых изменениях; индуцирует резистентность к действию глюкокортикостероидов; стимулирует выработку фактора свертывания крови XII, приводя тем самым к развитию потенциально фатальных осложнений, таких как тромбоэмболия лёгочной артерии и ишемический инсульт.

***Заключение.*** В настоящем обзоре литературы проведен структурированный анализ многокомпонентной роли TGF-β в патогенезе постковидного синдрома, фиброза легкого при COVID-19, опухолей дыхательной системы, хронической обструктивной болезни легких, бронхиальной астмы. Обосновано возможное использование TGF-β как биомаркера тяжелой и средней степени тяжести COVID-19.

**Ключевые слова:** *трансформирующий фактор роста β; COVID-19; тучные клетки; хроническая обструктивная болезнь легких; опухоли*

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# Role of Transforming Growth Factor-β in Pathogenesis of Pulmonary Fibrosis in COVID-19, Post-COVID Syndrome, Oncological and Chronic Inflammatory Lung Diseases

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***ABSTRACT***

***INTRODUCTION:*** Persistent post-COVID syndrome is the persistent physical, medical and cognitive sequelae of coronavirus disease 2019 (COVID-19), including persistent immunosuppression, pulmonary, cardiac and vascular fibrosis which lead to increased mortality and impair the quality of life of patients.

***AIM:*** To analyze the completed foreign and domestic studies on the pathophysiology of transforming growth factor-β (TGF-β) in conditions of COVID-19, post-COVID syndrome, oncological and chronic inflammatory lung diseases.

Mast cells are among the main producers of inflammatory cytokines in COVID-19, their stimulation leads to the release of many proinflammatory cytokines, such as interleukin 1β, tumor necrosis factor α, interleukin 6, and also TGF-β. The basis of the pathogenesis of post-COVID syndrome is the overexpression of TGF-β leading to a prolonged state of immunosuppression and fibrosis. TGF-β acts as a tumor suppressor inhibiting proliferation and inducing apoptosis in the early stages of oncogenesis; plays an important role in most cellular biological processes leading to remodeling of the airway structures; is involved in epithelial changes, in subepithelial fibrosis, remodeling of smooth muscle of airways and in microvascular changes; induces resistance to glucocorticosteroids; stimulates the production of blood coagulation factor XII, thereby leading to development of potentially fatal complications, such as pulmonary embolism and ischemic stroke.

***CONCLUSION:*** In this literature review, a structured analysis of a multicomponent role of TGF-β in the pathogenesis of post-COVID syndrome, pulmonary fibrosis in COVID-19, tumors of respiratory system, chronic obstructive pulmonary disease, bronchial asthma, is given. A possible use of TGF-β as a biomarker of severe and moderate degree of COVID-19 is substantiated.

**Keywords:** *transforming growth factor β; COVID-19; mast cells; chronic obstructive pulmonary disease; tumors*

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ECO•VECTOR

## LIST OF ABBREVIATIONS

COPD — chronic obstructive pulmonary disease
COVID-19 — Coronavirus Disease 2019
ECM — extracellular matrix
ERK — extracellular signal-regulated kinase
FDP — fibrin degradation products
FXII — factor XII (factor XII, Hageman factor)
Ig — immunoglobulin
IL — interleukin
LAP — latency associated peptide
LLC — large latent complex
LTBP — latent transforming growth factor β binding protein
NK cells — natural killer cells
PPBP — pro-platelet basic protein
RAGE — receptor for advanced glycation end products
SARS-CoV-2 — Severe Acute Respiratory Syndrome-related Coronavirus 2
SMAD — Small Mothers Against Decapentaplegic
suPAR — soluble urokinase plasminogen activator receptor
TGF-β — Transforming Growth Factor β
TNF-α — Tumor Necrosis Factor α

## INTRODUCTION

Persistent post-COVID syndrome, also referred to as long COVID-19 (Coronavirus Disease 2019), is a pathological condition that involves persistent physical, medical and cognitive sequelae following COVID-19, as well as pulmonary, cardiac and vascular fibrosis resulting in increased mortality and severely worsening the quality of life. The basis of the pathogenesis of post-COVID syndrome is believed to involve overexpression of transforming growth factor β (TGF-β), which leads to prolonged state of immunosuppression and fibrosis [1].

Acute respiratory distress syndrome includes three overlapping phases: exudative, proliferative and fibrotic [2]. The exudative phase is characterized by release of proinflammatory cytokines, such as interleukin (IL) 1β, tumor necrosis factor α (TNFα), IL-6; inflow of neutrophils and disruption of endothelial-epithelial barrier, leading to alveolar filling and development of respiratory distress syndrome [3]. The exudative phase is followed by the fibroproliferative phase with accumulation of fibrocytes, fibroblasts and myofibroblasts in the alveolar compartment leading to excessive deposition of matrix components including fibronectin, collagen I and collagen III in the lung [4].

L. V. Wismans, et al. (2023) showed a significant increase in tryptase- and chymase-positive mast cells in SARS-CoV-2-infected lung tissue, as well as in the expression of genes involved in fibrosis and thrombosis, receptor for advanced glycation end products (RAGE) and pro-platelet basic protein (PPBP), compared to tissues of patients infected with the influenza virus [5].

The TGF-β signaling pathway is a cascade of signals from the membrane to the nucleus through receptor-mediated activation of transcription factors [6]. As ligands, cytokines bind to two pairs of transmembrane serine/threonine protein kinases, causing activation of receptor and phosphorylation of SMAD (Small Mothers Against Decapentaplegic) transcription factors [6].

TGF-β is an evolutionarily preserved pleiotropic factor, which regulates a multiplicity of biological processes, including tissue regeneration, immune reactions and oncogenesis [7]. TGF-β is essential for lung organogenesis and homeostasis as evidenced by genetically modified mouse models [7]. TGF-β has a decisive significance in epithelial-mesenchymal interactions in the lung branching morphogenesis and alveolarization [7]. Secretion of TGF-β alone is insufficient for its bioavailability. TGF-β is activated by several mechanisms, including proteolysis, low pH, reactive oxygen species and thrombospondin-1 [7]. TGF-β is also activated by specific integrins, such as α Vβ6 integrin that senses stretch or stiffness of extracellular matrix (ECM) [8].

### Structure and Functions of TGF-β

The TGF-β cytokine superfamily contains more than 30 structurally related polypeptide growth factors, including TGF-β1, TGF-β2, TGF-β3, etc. [9]. TGF-β peptides are synthesized as latent precursors and are cleaved to form a mature TGF-β dimer noncovalently bound to a latency associated peptide (LAP) [7]. LAP of TGF-β1 or TGF-β3 has an integrin recognition motif, an arginine-glycine-aspartic acid sequence, and binds to integrins [7]. The secreted TGF-β and LAP complex is bound by latent TGF-β binding protein (LTBP), which forms a large latent complex (LLC) [7]. LTBP is a matrix protein incorporated in the ECM, and latent TGF-β (TGF-β-LAP complex) can accumulate in the extracellular environment [10]. Integrin-dependent binding of contracting myofibroblasts induces a conformational change in LAP, which releases active TGF-β from the ECM [11].

The state of the ECM determines the direction of TGF-β activation, which sets a mechanical threshold for profibrotic activity of myofibroblasts [11]. The influence on this mechanic threshold may have important

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consequences for the restoration of normal versus fibrous tissue [11].

The SMAD protein family is a canonical activation pathway proteins in which TGF-β is identified as TGF-β receptor II [12]. TGF-β receptor II and TGF-β receptor I then form a heteromeric complex [12]. Activated TGF-β receptor I phosphorylates receptor-regulated SMAD proteins and promotes the binding of the complex to receptor-regulated SMAD protein, common SMAD and SMAD4 mediator, forming a trimeric complex, which is translated into the nucleus and aggregates there as a transcription factor to regulate target gene expression [13]. SMAD2 and SMAD3 are considered the most important TGF-β mediators in tissue fibrosis and oncogenesis [14]. SMAD6 and SMAD7 are considered as regulators of the processes of stimulation of TGF-β-mediated fibrosis and oncogenesis [14]. In endothelial cells, the ECM protein thrombospondin-4 is activated in response to TGF-β1 and mediates the effect of TGF-β1 on angiogenesis [14].

All pathways and subsequent cascades that are activated by TGF-β through phosphorylation, acetylation, sumoylation, ubiquitination, with participation of protein–protein interactions, are collectively referred to as non-SMAD-related signaling pathways [15]. Non-SMAD signaling proteins share three common mechanisms of TGF-β activation: non-SMAD signaling proteins directly modify (e. g., phosphorylate) SMADS thus modulating the activity of central effectors; non-SMAD signaling proteins directly interact with other signaling proteins (e. g., kinases) and modulate their activity thus transmitting signals through other pathways; TGF-β receptors directly interact with or phosphorylate non-SMAD proteins thus initiating parallel signaling that cooperates with the SMAD pathway in generating physiological responses [16]. The extracellular signal-regulated kinase (ERK) signaling pathway, for example, influences embryonic development, neural tissue development, epithelial-mesenchymal transition (transformation), and promotes fibrosis and metastasis of cancer [17, 18]. In addition, it was shown that introduction of TGF-β1 in early stem cell culture in the presence of IL-3 increased subsequent proliferation of erythroblasts [19]. TGF-β induces overexpression of the fibrillar α2 collagen protein (I) [20]. TGF-β1 induces production of chemokine CXCL16 and leukemia inhibitory factor in osteoclasts, which modulate recruitment of osteoblasts to restore bone lost during the resorptive phase of bone turnover [21]. TGF-β1 and TGF-β2 are involved in airway remodeling by stimulating the phenotypic change of fibroblasts to myofibroblasts [22].

## Involvement of TGF-β in Pathogenesis of Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in economically developed countries. It is characterized by derangement of the alveolar structure, airspace restriction, and also by airway alterations with resulting hypersecretion of mucus, peribronchial fibrosis and alveolar tissue remodeling [23]. Various chronic respiratory diseases, such as bronchial asthma (BA), COPD have a common feature — susceptibility to exacerbations, often associated with viral infections, which lead to further impairment of gas exchange in lungs and hospitalization [23]. TGF-β1 is believed to play an important role in most biological processes leading to remodeling of the airway structures. It has been shown to be involved in epithelial changes, subepithelial fibrosis, airway smooth muscle remodeling and microvascular changes [23]. Thus, increased expression of TGF-β1 has been recorded in the epithelium of small airways and basement membranes of the bronchial network in patients with COPD [23].

TGF-β1 level in blood serum have been found to be higher in patients with a mild stable COPD than in smokers of the control group without COPD [23]. These data reflect stage-dependent association with TGF-β1 in stable COPD [23]. In contrast to TNF-α, TGF-β1 is activated at early COPD stage and can be used as serum biomarker of COPD severity [23]. Stretch and stiffening of the extracellular matrix decrease the threshold for TGF-β1 activation through increase in the mechanical resistance to cell pulling. Different elements of this mechanism may be pharmacologically targeted to interrupt the mechanical positive feedback loop of fibrosis including specific integrins and interactions with matrix proteins [24].

TGF-β1 predominantly increased in severe BA and correlated with the degree of airway obstruction [25]. In patients with mucoviscidosis (moderate fibrosis), TGF-β1 level was increased in bronchoalveolar lavage fluid and directly correlated with the airways neutrophil counts, impairment in the lung function, and hospitalization [26]. TGF-β1–3 are found in the airway epithelium of healthy people [27]. Increased TGF-β1 level may be associated with BA severity, upon that, it was shown by immunofluorescence microscopy that eosinophils produce up to 50% of the detected TGF-β1 [27].

Exacerbations of asthma and COPD are commonly associated with respiratory syncytial virus, rhinovirus, and influenza A virus [28]. The ensuing airway

inflammation is resistant to the anti-inflammatory effects of glucocorticoids [29]. Viral infection evokes increase in TGF-β activity, which attenuates the effects of glucocorticosteroids in human airway epithelial cells via activation of the activin-like receptor kinase-5 of TGF-β type I receptor [29].

Thus, pleiotropic signaling pathways activated by TGF-β are not only involved in complex pathological mechanisms, but also reduce the effectiveness of anti-inflammatory therapy in BA and COPD.

## Involvement of TGF-β in Pathogenesis of Tumors of Respiratory System

A. Korkut, et al. (2018) presented a comprehensive analysis of gene alterations, which modulate transmission of TGF-β-SMAD-mediated signals in tumor samples across 33 cancer types in The Cancer Genome Atlas. Focusing on genes that encode mediators and regulators of TGF-β signals transmission, at least one genomic alteration (mutation, homozygous deletion or amplification) was found in 39% of cases, with highest frequency in gastrointestinal cancer [30]. Alterations in TGF-β superfamily positively correlated with expression of metastasis-associated genes and with decreased survival [30].

TGF-β-induced epithelial-mesenchymal transformation leads to increase in the number of mesenchymal cells that are prone to metastasizing and are more resistant to both cytotoxic chemotherapy and targeted therapy [31]. Phenotypic alterations, such as epithelial-mesenchymal transformation and pharmacokinetics of chemotherapeutic drugs with TGF-β, were implicated in cytotoxic drug resistance [31]. Moreover, activation of TGF-β-SMAD-mediated transcription weakens the antitumor immunity by preventing differentiation, proliferation and activation of T-cells [31]. TGF-β enhances expression of CD8+ T-cells apoptosis protein via SMAD3-dependent mechanism [31]. Selective targeting of immunosuppressive activity of TGF-β may be proposed as therapeutic intervention to improve clinical response to standard treatment in lung cancer [31].

SMAD4 is a known positive regulator of canonical TGF-β signaling that facilitates R-SMAD translocation to the nucleus to initiate transcription [31]. The role of this regulatory function of SMAD4 is relevant for individuals with inherited SMAD4 defects, which may prevent natural killer (NK) cells from effectively controlling tumor cells and may contribute, at least in part, to their susceptibility to polyposis and colon cancer [31]. Y. Wang, et al. (2018) also showed that SMAD4 is able to regulate NK cell-mediated antitumor and antiviral innate immune responses [32].

Adaptive immunity is one of three major immune pathways involved in the pathogenesis of tumor diseases, and is also regulated by TGF-β signaling, which can control adaptive immunity by directly stimulating T cell expansion, activating CD4+ T cell responses, and controlling effector T cell function [33]. Besides, TGF-β similarly controls the development and functions of the innate immunity via inhibiting NK cells and regulating proliferation of macrophages and granulocytes [33]. Mutations of SMAD4 cells contribute to the dysregulation of homeostasis by NK cell and increase tumor cell metastasis [33]. Studies have shown that TGF-β-induced immune tolerance and inflammatory responses can be corrected by ionizing radiation in combination with hyperthermia and checkpoint inhibitor therapy [33].

## Involvement of TGF-β in Pathogenesis of COVID-19 and Post-COVID Syndrome

Y. Wang, et al. (2021) conducted a study involving 153 patients (43% men; mean age 56.5 ± 18.3 years) with COVID-19 from 4 hospitals of Guangdong and Hubei provinces. Patients were divided into three groups: 47 (18.5%) severe patients including extremely severe ones on mechanical ventilation, 70 (58%) — moderately severe and 36 (23.5%) patients with a mild form. In all patients, blood samples were taken during hospitalization. First, serum levels of TGF-β1 and COVID-19-specific antibodies were analyzed. Serum levels of TGF-β1 in patients with severe and moderate COVID-19 significantly increased from day 1 to day 10 after the onset of symptoms, while circulating TGF-β1 levels in recovering patients were similar to those in healthy subjects. Compared to patients with severe COVID-19, in patients with moderate form, the TGF-β1 level increased most significantly within the first 30 days ($p < 0.01$) and declined in the subsequent 10 days ($p < 0.05$) [34].

Serum antibody and cytokine levels were further investigated in COVID-19 patients at different stages of the disease, and TGF-β1 levels were lower in patients with mild degree than in patients with moderate and severe degree [35]. This is the first study to observe changes in TGF-β1 and immunoglobulins (Ig) A, G, and M levels in patients with different severity of COVID-19 disease. The results of this study suggest that elevated levels of the IgA isotype switch factor TGF-β1 are responsible for the pathological effects of IgA. TGF-β1 has also been considered as an important factor associated with advanced pulmonary fibrosis in SARS and MERS. The increased TGF-β1 levels in patients with severe and moderate COVID-19 may be due to the large volume of infectious lesions in the lung parenchyma, which may produce increased amounts of TGF-β1 during

viral infection. Besides, TGF-β is also produced by neutrophils infiltrated into the lung tissue and activated by COVID-19 infection, as well as by macrophages produced in apoptosis of bronchial epithelial cells, pneumocytes, and T lymphocytes [35].

SARS-CoV-2 virus and subsequent strong immune and inflammatory reaction, as well as dysregulation of coagulation and fibrinolysis pathways, evoke massive activation of latent (inactive) TGF-β in the lungs, as well as of latent TGF-β pool in patients' blood. SARS-CoV-2 causes massive increase in infiltration of lungs with neutrophils that release stored TGF-β, which may be activated by elastase in neutrophils. TGF-β in itself can be a potent chemokine-like molecule, recruiting more neutrophils into lungs, forming a positive feedback loop, which causes apoptosis of bronchial epithelial cells, pneumocytes and T-lymphocytes. Besides, the virus may also lead to death of neutrophils [36]. More macrophages migrate and infiltrate into lungs, where they engulf and digest apoptotic cells [37]. This also leads to production and secretion of large amounts of latent (and active) TGF-β into lungs [35]. The produced latent TGF-β can be further activated by local proteases such as furin, plasmin and elastase, reactive oxygen species, matrix metalloproteases and integrins such as αVβ6 [35]. Angiotensin 1–7 can inhibit expression of TGF-β and collagen, contributing to potential attenuation of airway remodeling in a severe course of COVID-19 [38].

S. Ongchai, et al. (2018) showed that TGF-β1, through enhanced expression of hyaluronan synthase-2, participates in regeneration of hyaline cartilage, which contains collagen and hyaluron [39]. Hyaluron is capable of absorbing large amounts of water, which may also explain accumulation of fluid in lungs of COVID-19 patients [40]. In COVID-19, there is also increase in the levels of IL-6, IL-1β, TNF-α, granulocyte colony-stimulating factor or interferon-γ-induced protein 10 in plasma [41].

Angiogenesis and coagulation in COVID-19 are considered not only as a manifestation of respiratory infection, but also as a hematological pathology due to its significant impact on the hematopoietic system [42]. Patients hospitalized with COVID-19, as a rule, are characterized by a high incidence of thromboembolic complications [43].

TGF-β stimulates the production of coagulation factor XII (FXII, Hageman factor). FXII is a serine protease [44]. Under the influence of FXII, peripheral blood mononuclear cells acquire a reparative phenotype of M2 macrophages, as evidenced by increased secretion of TGF-β, IL-4, IL-8, IL-10 [44]. It has been shown that FXII promotes the differentiation of naive T helper (Th) cells into Th17-type cells [44]. Activated FXII initiates the intrinsic coagulation pathway and the complement system, leads to cleavage and thus activation of plasma kallikrein, triggers fibrin formation through activation of factor XI and activates the complement pathway [45].

Levels of D-dimer, high-sensitivity cardiac troponin I, serum ferritin, lactate dehydrogenase and IL-6 increased with increasing severity of the disease [46]. A sharp pre-mortem rise of D-dimer level was recorded, reflecting inflammatory and procoagulant status of COVID-19 [43].

Antithrombin levels in COVID-19 patients were lower than in the control group ($p < 0.001$). The levels of D-dimer, fibrin degradation products (FDP), and fibrinogen were significantly higher in all SARS-CoV-2 cases than in healthy individuals [47]. Upon that, D-dimer and FDP values were higher in patients with severe SARS-CoV-2 infection than in patients with milder forms [47]. Compared with healthy individuals, prothrombin time activity was lower in patients with SARS-CoV-2 [47]. Thrombin time in critically ill SARS-CoV-2 patients was also shorter than in the control group [47]. Blood coagulation function in SARS-CoV-2 patients was significantly impaired compared with healthy individuals, but monitoring D-dimer and FDP values may be useful for early detection of severe cases [47].

Elevated levels of D-dimers in the blood suggest endothelial activation [48]. The soluble urokinase plasminogen activator receptor (suPAR), which is associated with the endothelium, can be cleaved early in the disease, leading to an increase in the amount of its soluble analogue [48].

Mast cells are known to synthesize various pro-fibrotic factors, including tryptase, chymase, histamine, leukotrienes, renin, and TGF-β1 [49, 50]. Our research team has shown an altered distribution of mast cells and their activation in the affected lung tissues of COVID-19 patients with different stages of alveolar damage [51]. Considering the possibility of TGF-β1 production by mast cells when they express certain proteases, such as chymase, it seems interesting to study the profile of mast cells in COVID-19 patients and consider them as targets in the treatment of both the coronavirus disease itself and its consequences. Figure 1 shows the role of TGF-β in the pathogenesis of pulmonary fibrosis in COVID-19 and post-COVID syndrome.

## CONCLUSION

As follows from the presented material, transforming growth factor β is the basis of the pathogenesis of post-COVID syndrome, its overexpression leads to a long-standing state of immunosuppression and fibrosis, besides, transforming growth factor β is involved in

the pathogenesis of tumors, diseases of respiratory system, such as chronic obstructive pulmonary disease, bronchial asthma.

Transforming growth factor β plays an important role in most cellular biological processes, leading to remodeling of the airway structures, and is also involved in epithelial changes, subepithelial fibrosis, airway smooth muscle remodeling, and microvascular changes. Transforming growth factor β controls the development and function of the innate immune system by inhibiting natural killer cells and regulates the proliferation of macrophages and granulocytes, and acts as a tumor suppressor by inhibiting proliferation and inducing apoptosis in the early stages of oncogenesis.

Selective impact of transforming growth factor β on the immunosuppressive activity can be proposed as a therapeutic intervention to improve the clinical response to standard treatment methods in lung cancer. Transforming growth factor β can also be considered as a diagnostic marker and pharmacological target in treatment of a number of pathological conditions. Transforming growth factor β can be a reliable biomarker for identifying patients with severe and moderate course of coronavirus disease 2019.

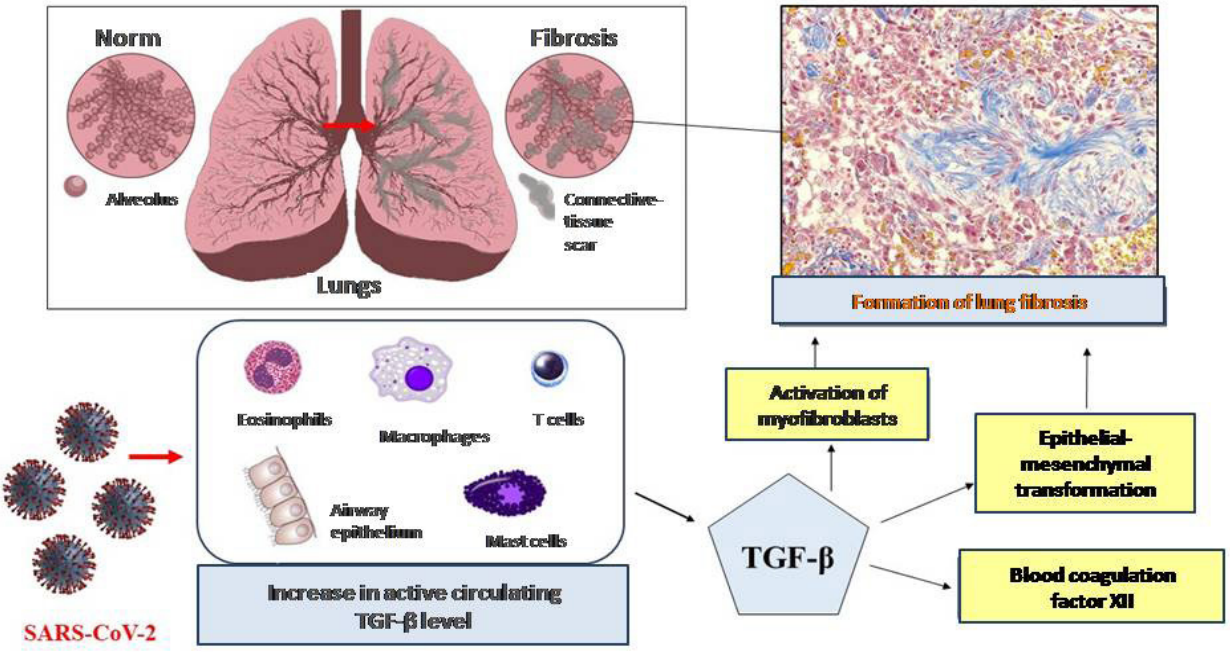


**Fig. 1.** Role of TGF-β in the pathogenesis of lung fibrosis in COVID-19 and post-COVID syndrome (authors' scheme, modified by [27]).

*Comments:* SARS-CoV-2 causes a cytokine storm, which leads to production and secretion of large amounts of latent and active transforming growth factor-β into lungs, which causes tissue fibrosis and impairment of the lung function. TGF-β is produced by eosinophils, macrophages, T cells and mast cells. In COVID-19 and post-COVID, increase in TGF-β is observed, leading to increase in the profibrotic activity of myofibroblasts and to diffuse damage. In the scheme, a photograph (authors' observation) of postmortem histological preparation of lungs of a patent with severe COVID-19 is presented, where connective tissue fibers (blue color) are identified by Picro Mallory staining [47]. Besides, TGF-β stimulates production of factor XII, which initiates the intrinsic coagulation pathway and complement system leading to thromboembolic complications.

*Notes:* COVID-19 — Coronavirus Disease 2019, FXII — factor XII (Hageman factor), SARS-CoV-2 — Severe Acute Respiratory Syndrome-related Coronavirus 2, TGF-β — transforming growth factor β.

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**Вклад авторов:** *Будневский А. В., Авдеев С. Н., Овсянников Е. С.* — концепция и дизайн исследования, редактирование; *Шишкина В. В., Алексеева Н. Г., Первеева И. М., Китоян А. Г., Антакова Л. Н., Юрченко А. С.* — подбор литературных источников, анализ данных, написание текста. Авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

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