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On the pathogenesis of COVID-19: the role of transforming growth factor beta

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ABSTRACT

Proteins of the transforming growth factor beta (TGF-β) family regulate numerous cellular processes that are essential in the pathogenesis of acute respiratory distress syndrome (ARDS), contributing to increased alveolar epithelial permeability, activation of fibroblasts, and extracellular matrix remodeling. TGF-β is involved in the pathogenesis of inflammatory respiratory diseases during the development of COVID-19. SARS-CoV-2 leads to complex immune responses that include the release of inflammatory cytokines, increased activity of mast cells, and the release of mast cell secretome, in particular profibrotic enzymes and cytokines, including TGF-β.

Tryptase- and chymase-positive mast cells play a major role in pulmonary fibrosis and embolism in COVID-19. Mast cell chymase is angiotensin-converting enzyme 2-independent due to extracellular formation of angiotensin II in the interstitium; it also activates TGF-β and other molecules, thereby playing a role in tissue remodeling. Mast cell β-tryptase increases the secretion of TGF-β1 by airway smooth muscle tissue and the expression of α-smooth muscle actin (α-SMA). TGF-β also induces the generation of mitochondrial reactive oxygen species (ROS), which enhances the production of ROS in lung fibroblasts. TGF-β is crucial for induing the synthesis of extracellular matrix components by fibroblasts.

The review is devoted to the structure of TGF-β, the sources of its secretion and functions, the mechanism of its involvement in the pathogenesis of COVID-19, and the possibility of its use as a prognostic marker of COVID-19 severity.

Keywords: transforming growth factor beta, mast cells, COVID-19, acute respiratory distress syndrome, inflammation

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К вопросу о патогенезе COVID-19: роль трансформирующего фактора роста бета

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РЕЗЮМЕ

Белки семейства трансформирующего фактора роста бета (TGF)β регулируют многочисленные клеточные процессы, которые играют важную роль в патогенезе острого респираторного дистресс-синдрома (ОРДС), способствуют повышению проницаемости альвеолярного эпителия, активации фибробластов и ремоделированию внеклеточного матрикса. Трансформирующий фактор роста бета участвует в патогенезе воспалительных заболеваний дыхательной системы при развитии COVID-19. SARS-CoV-2 приводит к сложным иммунным реакциям, которые включают высвобождение воспалительных цитокинов, повышение активности тучных клеток и высвобождение продуктов их секретома, в частности профибротических ферментов и цитокинов, в том числе TGF-β.

Триптаза- и химаза-положительные тучные клетки играют большую роль в легочном фиброзе и эмболии при COVID-19. Химаза тучных клеток является независимым от ангиотензинпревращающего фермента 2-го типа путем образования ангиотензина II внеклеточно в интерстиции, а также активирует TGF-β и другие молекулы, тем самым играя роль в ремоделировании тканей. Бета-триптаза тучных клеток увеличивает секрецию TGF-β1 гладкой мышечной тканью дыхательных путей и экспрессию α-гладкомышечного актина – α-SMA. TGF-β также индуцирует генерацию митохондриальных активных форм кислорода (АФК), что усиливает выработку АФК в фибробластах легких. TGF-β играет ключевую роль в индукции синтеза компонентов внеклеточного матрикса фибробластами.

Настоящий обзор посвящен рассмотрению структуры TGF-β, особенностям его секреции и функции. Представлен механизм его участия TGF-β в патогенезе COVID-19, а также возможности его использования в качестве прогностического маркера степени тяжести течения COVID-19.

Ключевые слова: трансформирующий фактор роста бета, COVID-19, тучные клетки, острый респираторный дистресс-синдром, воспаление

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The COVID-19 pandemic, which ended in May 2023, has lasted for more than three years. During this time, research and discoveries in the field of immunology made a breakthrough. COVID-19 affected more than 700 million people around the world causing more than 6.9 million confirmed deaths [1]. One of the long-term manifestations of COVID-19 that follows an acute phase of infection is post-COVID-19 syndrome.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, can trigger complex immune responses, such as activation of proinflammatory cytokines, an increase in mast cell (MC) degranulation, and release of MC compounds. [2, 3].

The receptor for SARS-CoV2 is angiotensin-converting enzyme 2 (ACE2), which binds to spike protein on the surface of SARS-CoV2. MCs synthesize ACE2 and tryptase contributing to the development of cytokine storm with

high levels of proinflammatory cytokines, including tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), IL-1β, thymic stromal lymphopoietin (TSLP), and others. [1, 4]. MCs are activated by SARS-CoV-2 ribonucleic acid (RNA) through the retinoic acid induced 1 (RAI-1) protein, toll-like receptor (TLR)-3, TLR-7, and TLR-8 (TLR). High concentrations of TNFα have been reported both in plasma and tissues of patients with COVID-19 [1, 4].

The baseline expression of ACE2 mRNA in lungs is quite low compared to other organs, but it increases in alveolar cells after SARS-CoV-2 infection. [5]. ACE2 is cleaved by transmembrane serine protease 2 (TMPRSS2) and a disintegrin and metalloprotease 17 (ADAM17), facilitating COVID-19 penetration into cells of the patient. [5]. SARS-CoV-2 increases the level of ACE2 mRNA, transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and fibronectin (FN) [5]. Consequently, binding of SARS-CoV-2 to ACE2 leads to an increase in transcription of genes associated with lung fibrosis [5].

A rise in the number of MCs influences rather high frequency of COVID-19-associated pulmonary embolism, since MCs were reported to induce thrombosis through activation of coagulation factors and thrombocytes. Tryptase- and chymase-positive MCs play a significant role in pulmonary fibrosis and embolism in COVID-19 [3]. Chymase is ACE2-independent due to formation of angiotensin II (AngII); it also activates TGF-β and other molecules and induces tissue remodeling. Chymase-associated formation of AngII occurs extracellularly in the interstitium [6].

FEATURES OF THE STRUCTURE AND SYNTHESIS OF TGF-β

Proteins of the TGF-β family are present in all multicellular organisms and play an essential role in development of organs, wound healing, immune responses, and oncogenesis [7–11]. Each of TGF-β-1, -2, and -3 (hereinafter collectively referred to as TGF-β, unless indicated otherwise) are secreted either as the small latent complex (SLC) which consists of a bioactive homodimer non-covalently associated with its pro-peptide (latency-associated protein; LAP) or as a large latent complex (LLC) in which the SLC is covalently bound to LTBP-1, -3, or -4. Whereas LTBP-1 and - can associate with all TGF-β isotypes, LTBP-4 binds only to TGFβ-1 and at a lower affinity than the other LTBPs [10, 12–14].

The LTBPs form latent complexes with TGF-β by covalent bonds to the TGF-β pro-peptide (LAP) through disulfide bonds in the endoplasmic reticulum [9]. LAP in turn is cleaved from the mature TGF-β precursor in the trans-Golgi network, but LAP and TGF-β remain strongly bound through non-covalent interactions [9, 15]. It is important to note that each monomer of LAP consists of a number of relatively rigid α-helices and β-sheets, but the active cytokine is held in place by multiple contacts with a single flexible loop, which has been termed the latency lasso and effectively holds the active TGF-β [8]. As long as this lasso maintains close interactions with the active cytokine, TGF-β can be stored in the extracellular space with almost no evidence of active TGF-β signaling or cellular responses [8].

LTBP were originally considered to play a role in maintaining TGF-β latency and directing the latent growth factor to the extracellular matrix. However, LTBP-1 also participates in TGF-β activation by integrins and may also regulate its activation by proteases and other factors [9]. LTBP-3 is involved in skeleton formation, including tooth formation. LTBP-2 and LTBP-4 are identified as TGF-β-independent activators that have important functions in the regulation of TGF-β and stabilize bundles of microfibrils and regulate the assembly of elastic fibers [9]. Genetic ablation of both short and long isoforms of LTBP-4 leads to an increase in TGF-β activity in lungs, which is consistent with the previous observation that LTBP-4L interacts with TGF-β in a more effective way [12]. However, significant amounts of LTBP-1 and LTBP-4 are secreted without SLS, just like LTBP-2, which cannot interact with SLC [12]. TGF-β together with LAP can form complexes with LTBP-1, which are generated by fibroblasts [16].

Activation of TGF-β1 and LAP cleavage are induced by an acidic environment or are implemented by extracellular proteases, including thrombospondin-1, plasmin, cathepsin D, matrix metalloproteinase (MMP)-2 and -9, furin convertase, and integrins [10]. The LAP domain of TGF-β has the RGD sequence (arginine – glycine – aspartic acid), which mediates binding to integrins [13].

Alpha V beta 6 (avβ6) integrin was demonstrated to activate TGF-β1, and alpha V beta 8 (avβ8) integrin was shown to activate TGF-β1 via membrane-bound MMPs [10]. The molecules of the integrin family, which interact with RGD, can activate latent TGF-β1 and TGF-β3 [17]. The αvβ1 heterodimer has recently been shown to be a regulator of latent TGF-β in fibrosis, and the integrins avß5 and α51 participate in the activation of myofibroblasts [18]. Alpha V beta 8 integrin is a cell surface receptor for the LAP of the multifunctional cytokine TGF-β [19]. Altered expression of the integrin subunit β8 (ITGB8) is found in human chronic obstructive pulmonary disease, cancers, and cerebrovascular malformations [19]. The inflammatory process can change the level of TGF-β through specific mediators that influence gene transcription [19]. Thus, IL-1β increases the accessibility of transcription factors to the ITGB8 promoter in lung fibroblasts through chromatin remodeling [19].

Signaling of the TGF-β superfamily can be mediated through the Smad- and non-Smad pathways, in particular through the activation of mitogen activated protein kinase (MAPK), including extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK); as well as through the phosphoinositide 3-kinase (PI(3)K)/Akt pathway, and the NF-κB pathway [10].

In addition to the non-proteolytic latent TGF-β activation mechanism, proteolytic mechanisms also take part in that process. They include two types of proteases: glycoside-containing proteases (N-glycanase and neuraminidase) and serine proteases (plasmin, cathepsin D, and MMPs) [20, 21].

LTBPs are structurally related to the fibrillin family of proteins, which includes fibrillin-1 and fibrillin-2. Fibrillin-1 is an inhibitor of TGF-β signaling and an integral component of microfibrils [22]. Microfibrils cover the core of elastic fibers and contribute to the temporal and spatial regulation of TGF-β activation [16]. Microfibrils consist of fibrillins, which are associated with glycoproteins and protein microfibrils. These microfibrils bind TGF-β, and fibrillins are the key components that provide scaffolds for elastic fiber formation [23].

Fibrillin-1 expression persists throughout life, while the expression of fibrillin-2 is limited to the development of fetal tissues [13]. Furthermore, fibrillin-1 together with the bound molecules, masks fibrillin-2 epitopes, blocking its bioactivity [16]. Fibrillins function as scaffolds for the elastic fiber formation, that contribute to the maintenance of tissue homeostasis and regulate growth factor signaling in the extracellular space [14]. Fibrillin-1 is a modular glycoprotein that consists of 7 latent TGF-β-binding domains and mediates cell adhesion through integrin binding to the RGD motif in its 4th domain [14]. The activation of integrin-mediated TGF- is quite important for immune system, oncogenesis, and functioning of fibroblasts [11]. Both avβ6 and avβ8 integrins regulate TGF-β signaling by binding to a linear tripeptide depending on the tensile force created by the actin cytoskeleton [11].

L. Zilberberg et al. in their research in 2012 analyzed both *in vitro* and *in vivo* the role of fibrillin microfibrils in the synthesis of LTBP-1, -3 and -4 [22]. The authors showed that fibrillin-1 is important for integration of LTBP-3 and LTBP-4 into the extracellular matrix (ECM), but not for LTBP-1, because the presence of fibronectin is important for the association of LTBP-1 with ECM [22].

TGF-β AS A REGULATOR OF NUMEROUS CELL FUNCTIONS

TGF- β is produced by fibroblasts, epithelial, endothelial and smooth muscle cells in the airways [24]. In addition, TGF-β induces the synthesis of various ECM proteins by fibroblasts, such as collagens, elastin, proteoglycans, and fibronectin [24]. TGF-β is expressed by infiltrated eosinophils, lymphocytes, and MCs [24]. Lymphocytes and thrombocytes also contain TGF-β [24].

Latent TGF-β s highly expressed in airway and alveolar epithelia, alveolar macrophages, and ECM of the lungs, where the inhaled microorganisms face host body defense mechanisms during their pulmonary phase [26]. Its maximum concentration in the respiratory system is observed in the bronchial epithelium [24]. Enhanced TGF-β1 signaling during inflammation initially leads to local suppression of the host immune system via direct inhibition of effector immune cells like T cells and dendritic cells [26].

TGF-β plays a key role in inducing the production of ECM components by fibroblasts [23]. TGF-β itself plays a significant and complex role in the immune response of the respiratory tract, mediating various proinflammatory or immunosuppressive effects [27].

TGF-β1 stimulates the attraction of inflammatory cells in the airways and stimulates the secretion of additional growth factors and proinflammatory cytokines [27]. And vice versa, TGF-β1 can suppress both proliferation of lymphocytes and production of particular cytokines [27]. Thus, IL-13 interacts with IL-4, inducing alternative activation of M2 macrophages. That interaction promotes the release of TGF-β1 platelet-derived factor [28]. This phase is characterized by short-term expansion of resident fibroblasts, formation of a temporary matrix, and proliferation of airway progenitor cells and type 2 pneumocytes [28].

TGF-β plays an essential role in regulating ECM components in the airways: it increases synthesis of proteins, such as fibronectin, enhances antiprotease activity, stimulates expression of desmosomal proteins by bronchial epithelial cells, which promotes activation of proteins involved in intercellular junctions and contributes to the formation of the basement membrane in alveolar epithelial cells [29]. Finally, TGF-β contributes to the mechanisms involved in the control of epithelial cell growth and differentiation. For example, TGF-β induces differentiation of normal bronchial epithelial cells, regulates growth of cells via inhibition of cell proliferation, and induces apoptosis of epithelial cells in the lungs [29].

TGF-β regulates the expression of proteins involved in the fibrous cascade, including the regulation of expression and activity of extracellular remodeling proteases, including MMPs, tissue inhibitors of metalloproteinases, and endothelin-1 expression [10]. Endothelin-1 contributes to persistent fibrosis by inducing fibroblasts to produce and secrete TGF-β by ECM and also regulating the activity of the Rho family of GTPases, which take part in TGF-β-induced fibrosis [10]. In general, TGF-β is a key regulator of ECM production and, therefore, enhanced TGF-β signaling is a crucial factor in progression of fibrosis [10].

TGF-β has been shown to suppress the proliferation of CD4+ T cells via inhibition of the autocrine production of IL-2 [15]. In CD8+ cytotoxic T cells (TC cells), TGF-β-activated Smad proteins cooperate with activating transcription factor 1 (ATF1), suppressing the expression of interferon-γ and cytolytic factors, such as perforin, granzyme, and Fas-ligand, thus inhibiting the anti-tumor activity of these cells. TGF-β also modulates proliferation and other functions of B cells, natural killer cells (NK-cells), monocytes, macrophages, and granulocytes. TGF-β plays a pleiotropic role in lymphocyte regulation, and this is especially apparent in T cells [15].

TGF-β1 induces alpha-smooth muscle actin (α-SMA) and collagen synthesis in fibroblasts both *in vivo* and *in vitro* and also plays a significant role in tissue repair and the development of fibrosis [30]. During these processes, fibroblasts differentiate into fibromyoblasts characterized by increased expression of α-SMA [30].

TGF-β1 suppresses plasmin and plasmin-mediated MMP activity in flexor tendon cells cultured *in vitro* via activation of PAI-1[21]. It is possible that TGF-β1 also suppresses MMP and plasmin activity in other ways, such as through the suppression of tissue-type plasminogen activators (tPA), urokinase-type plasminogen activators (uPA), and / or membrane-bound MMP expression in tenocytes [21]. TGF-β is aberrantly activated during the degradation of ECM because of high activity of MMP [12].

TGF-β1 and IL-6 have opposite effects on regulation of cathepsin B and L activity in A-549 human lung epithelial cells [29]. The proinflammatory cytokine IL-6 induced an upregulation of cathepsin L, whereas TGF-β1 suppressed cathepsin B and L expression. Cathepsins B and L are expressed cysteine proteinases that play an important role in lysosomal bulk proteolysis, protein processing, matrix degradation, and tissue remodeling [29].

M. Jain et al. in 2013 demonstrated that TGF-β triggers the production of mitochondrial reactive oxygen species (ROS), which in turn activates the transcription of nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4). That enhances the production of ROS in lung fibroblasts in patients with idiopathic and scleroderma-induced lung fibrosis [31].

FEATURES OF MOLECULAR INTERACTION OF TGF-β AND IMMUNOCOMPETENT CELLS IN COVID-19

The anatomy of the lungs is vulnerable to external stimuli and pathogens, and, as a result, inflammation, allergic reactions, and carcinogenesis take place. Increased regulation of TGF-β ligands is

observed in the majority of lung diseases, including pulmonary fibrosis, emphysema, bronchial asthma, and lung cancer [32]. Based on the published data, patients with COVID-19 or post-COVID syndrome may develop pulmonary fibrosis. The prognosis for this serious complication also deserves attention of medical professionals and the scientific community. The morphological characteristics of pulmonary fibrosis include thickening of the alveolar septa, collagen deposition, and fibroblast proliferation, as well as, diffuse inflammation.

After infection with COVID-19, the TGF-β pathway inhibits cell apoptosis and induces fibroblast proliferation and myofibroblast differentiation, developing pulmonary fibrosis [33]. In the early stage of SARS-CoV-2 infection, a number of inflammatory responses and dysregulation of the fibrinolytic and coagulation pathways can promote activation of the latent form of TGF-β in the blood and lungs [33].

TGF-β causes fibrosis, which is a common complication in patients with severe forms of COVID-19. Acute respiratory distress syndrome (ARDS) in COVID-19 patients can lead to terminal pulmonary fibrosis [34]. TGF-β activation promotes the differentiation of fibroblasts into myofibroblasts and also regulates remodeling of the fibrous component in ECM [34].

With the development of COVID-19, SARS-CoV-2 penetrates into the upper respiratory tract through ACE2 receptors, which are located on the surface of the pulmonary epithelium [35]. The virus infects type II pulmonary alveolar cells during their migration into the lower respiratory tract [35]. In patients with COVID-19, interstitial pulmonary edema occurs in the acute phase of ARDS, and the formation of hyaline membranes results from diffuse damage to the alveoli, while fibrosis of the interalveolar septa and fibroblast proliferation develop in the phase of chronic remodeling [28]. SARS-CoV-2 is supposed to increase the TGF-β concentration by reducing the regulation of the ACE2 receptor through its interaction with the spike protein. Consequently, as the regulation of ACE2 is decreased, the level of angiotensin II increases, and that enhances the activity of the TGF-β intracellular signaling pathway [36–39].

TGF-β has been shown to suppress the number of circulating NK-cells in patients with COVID-19 [26]. The activation of TGF-β increases the permeability of the endothelial and epithelial cells, which leads to an influx of fluids and proteins into the alveoli. This process worsens gas exchange in the lungs and results in arterial hypoxemia and respiratory failure [40]. Superficial proteins of epithelial and endothelial cells are surrounded by a dense mesh of glycans, called the epithelial / endothelial glycocalyx layer. Disruption of this layer is mediated by SARS-CoV2 [41].

Our research team showed the increase in MC activity and changes in their phenotype in lung tissues of patients who died from COVID-19 [42]. MC, located in close proximity to fibroblasts, are sensitive to mechanical stress in fibrotic lungs and, therefore, can be stimulated by breathing process in rigid and fibrous lungs [43, 44]. MC granules may contain large amounts of profibrotic enzymes and cytokines, such as TGF-β, IL-4, IL-10, IL-13, chymase, tryptase, and growth factors [43], which promote fibroblast activation [45].

Mast cell β-tryptase increases the production of TGF-β1 by airway smooth muscle and stimulates α-SMA secretion, leading to functional changes in muscle tissues [46]. TGF-β1 mediates the expression of genes involved into fibrotic process, including collagen, proteases, and fibronectin, through a Smad-dependent mechanism [27]. Airway smooth muscle cells (ASMCs) contain a lot of TGF-β1–3 [28]. Plasmin and serine protease regulate the production of a biologically active form of TGF-β by ASMCs as well as the release of extracellular TGF-β [24]. The release of TGF-β activated by plasmin induces autocrine synthesis of type I collagen by ASMC [24]. Macrophages are also important agents that contribute to lung fibrosis. The activation of TGF-β / Smad and IL-6 / STAT3 signaling pathways can be involved in the M1– M2 polarization transition of macrophages in cases of COVID-19 [47].

SERUM TGF-β LEVELS IN COVID-19

The most severe complication of SARS, caused by coronavirus infection, is pulmonary fibrosis, which develops in 45% of patients within 3 to 6 months after infection [48]. Increased expression of TGF-β in COVID-19 patients may be the cause of pulmonary fibrosis [49]. It was found that patients with ARDS with lower levels of TGF-β in the bronchoalveolar lavage fluid had fewer days

spent in intensive care units and mechanically ventilated [50].

Patients with COVID-19 have an increased level of TGF-β1 in their serum and plasma, and this correlates with the severity of their condition [26]. The level of immunosuppressive cytokines, such as TGF-β and IL-10, increased after SARS-CoV-2 infection and there was no correlation with gender [33]. Increased serum levels of TGF-β in the early days of COVID-19 infection may indicate the potential development of severe bleeding complications, including the need for intensive care and a risk of death.

S. Frischbutter et al. (2023) noted a significant increase in serum levels of TGF-β within the first two weeks after the onset of symptoms in COVID-19 patients [51]. This early increase of serum TGF-β impairs the ability of NK-cells to eliminate the cells infected with the virus [51]. Thus, patients with mild COVID-19 (n = 27) had concentrations of 165.4 pg / ml ± SD 105.4, patients with moderate COVID-19 (n = 11) had slightly higher levels of 240.6 pg / ml ± SD 150.2, and patients with severe COVID-19 (n = 25) had greater serum TGF-β levels of 416.3 pg / ml ± SD 161.7 ($p < 0.0001$) compared to patients with mild or moderate COVID-19 [51]. The authors suggest that patients with serum TGF-β levels of above 254.75 pg / ml are at high risk (92%) of progression of a severe form of COVID-19 infection [50]. TGF-β can be considered and recommended as a predictive marker of COVID-19 severity [51, 52].

A MODEL OF TGF-β INVOLVEMENT IN THE PATHOGENESIS OF COVID-19

A model of TGF-β activation in the development of COVID-19 is presented in the authors' scheme (Figure).

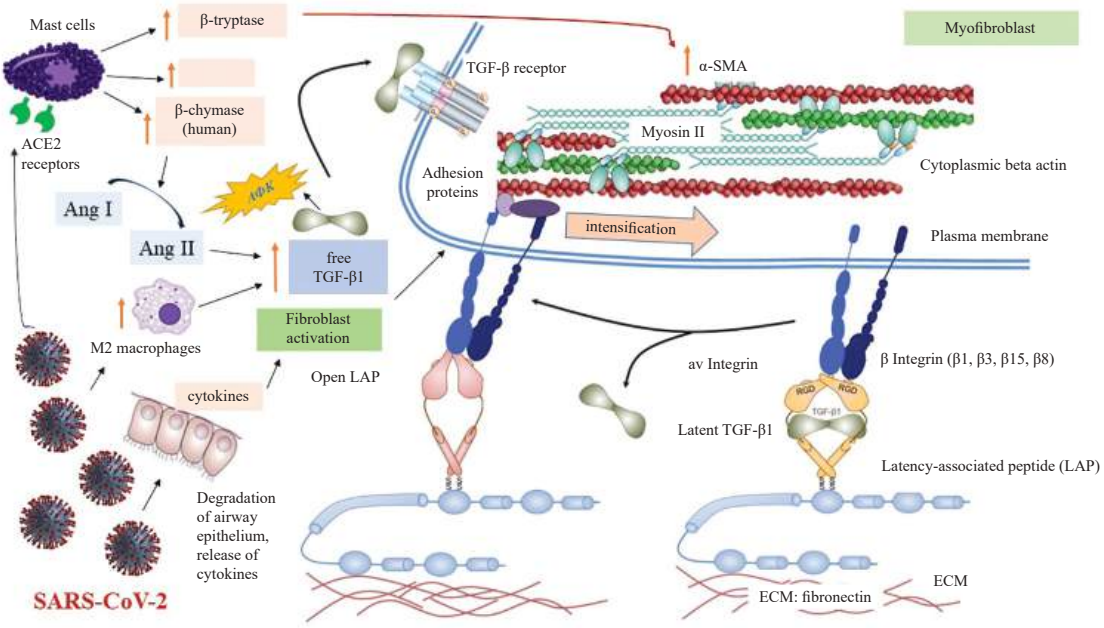

Figure. A model of TGF-β activation in the development of COVID-19 (authors' scheme modified according to [8])

Explanation: тhe receptor for SARS-CoV2 is ACE2, which binds to Spike protein on the surface of coronavirus. This interaction causes the release of cytokines by various cellular agents. With the development of COVID-19, the activity of MC and synthesis of their products increase, including profibrotic mediators, such as tryptase, chymase, and TGF-β. TGF-β induces the differentiation of fibroblasts into myofibroblasts. TGF-β also induces the production of mitochondrial ROS, which enhances their production in pulmonary fibroblasts.

MC chymase is the ACE2-independent pathway of Ang II formation in ECM. It also activates TGF-β and other molecules, thus contributing to tissue remodeling. Beta-tryptase of MC increases the production of TGF-β1 by fibroblastic differon and rises the expression of α-SMA.

TGF-β is produced in airway fibroblasts, endothelial and smooth muscle cells, then it is

accumulated in ECM as latent TGF-β (LTBP). LTBPs form latent complexes with TGF-β by covalently binding to the pro-peptide TGF-β, LAP, via disulfide bonds in the endoplasmic reticulum. Latent TGF-β1 activation from ECM is initiated by integrins through binding to the RGD sequence (arginine – glycine – aspartic acid) in the LAP – TGF-β domain. This activation is also induced by acidic pH or is carried out by extracellular proteases, such as thrombospondin-1, plasmin, cathepsin D, MMP-2, MMP-9, and furin convertase.

CONCLUSION

There is no doubt that TGF-β is involved in the pathogenesis of inflammatory diseases of the respiratory system in COVID-19. TGF-β regulates numerous cell processes, which play an important role in ARDS development, increases the permeability of the alveolar epithelium, activates fibroblasts, and promotes ECM remodeling. SARS-CoV-2 causes prolonged activation of immune cells, development of complex immune responses, and production of a large number of cytokines, including profibrotic enzymes, in particular, TGF-β.

Tryptase- and chymase-positive MCs play a significant role in the development of pulmonary fibrosis and pulmonary embolism in COVID-19, including through activation of the TGF-β pathway. MC chymase is the ACE2-independent pathway of Ang II formation in ECM. It also activates TGF-β and other molecules, thus contributing to tissue remodeling. Beta-tryptase of MC increases the production of TGF-β1 by airway smooth muscle cells and rises the expression of α-SMA. TGF-β also induces the production of mitochondrial ROS, which enhances their production in pulmonary fibroblasts.

TGF-β plays a crucial role in the regulation of airway ECM components: it increases the synthesis of proteins, such as fibronectin, enhances antiprotease activity, and stimulates the expression of desmosomal proteins by bronchial epithelial cells, which promotes the activation of proteins involved in intercellular junctions and the formation of the basement membrane of alveolar epithelial cells. Thus, the blood TGF-β level, considered by many scientists as a predicting marker of COVID-19 severity, has the potential to be used as a marker of fibrotic processes in other respiratory diseases.

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