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ПЕРСПЕКТИВЫ ЛЕЧЕНИЯ ИДИОПАТИЧЕСКОГО ЛЕГОЧНОГО ФИБРОЗА

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Prospects for Treatment of Idiopathic Pulmonary Fibrosis

Резюме

Идиопатический легочный фиброз (ИЛФ) является тяжелым прогрессирующим заболеванием легких неизвестной этиологии со средней распространенностью 15 на 100000 населения в мире. Различают спорадические, синдромальные и семейные случаи болезни. Спорадические случаи относятся к многофакторным заболеваниям и ассоциированы с возрастом, вирусными инфекциями, курением и вдыханием пыли, контактом с химическими реагентами и лекарствами, гастроэзофагальной рефлюксной болезнью. Выявлена ассоциация спорадического ИЛФ с аллельными вариантами генов *AKAP13, ATP11A, DPP9, DSP, IVD, IL1RN, FAM13A, MUC5B, SFTPC, SPPL2C, TERC, TERT, TOLLIP*. Синдромальный ИЛФ описан при синдроме Германского-Пудлака. Семейные случаи болезни обусловлены мутациями в генах, кодирующих белки сурфактанта (*SFTPC*), муцина (*MUC5B*), нуклеазу деаденилирования (*PARN*), участвующие в функционировании теломер (*RTEL1, TERC, TERT*). В 2000 году Американское торакальное сообщество рекомендовало глюкокортикоиды и цитостатики для лечения ИЛФ с целью воздействия на воспалительный процесс при активации фибробластов и их аккумулировании во внеклеточном матриксе легких. Эти рекомендации до сих пор используются практике, несмотря на публикации достоверных данных о повышенной смертности и случаев госпитализации пациентов с ИЛФ, принимающих преднизолон и азатиоприн. Согласно данным недавних метаанализов, наиболее эффективными в лечении ИЛФ являются пирфенидон (ингибитор синтеза факторов роста проколлагенов I и II) и нинтенадиб (ингибитор тирозинкиназы). Поскольку важную роль в этиопатогенезе болезни играют генетические факторы, перспективен поиск методов таргетной терапии с использованием в качестве мишеней специфических некодирующих РНК, изменения экспрессии которых не характерны для других бронхолегочных заболеваний. К ним относятся miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (уровень их снижается при болезни); miR-340, miR-424, miR-487b, miR-493, lncRNA AP003419.16, lncRNA AP003419.16 (повышенная экспрессия при ИЛФ).

Ключевые слова: *диагностика, идиопатический легочный фиброз, лечение, механизм развития, микроРНК, наследственность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a severe, progressive lung disease of unknown etiology with an average worldwide prevalence of 15 per 100,000. According to the etiology, IPF is classified into sporadic, syndromic, and familial cases. Sporadic cases refer to multifactorial diseases and are associated with age, viral infections, smoking and inhalation of dust, contact with chemicals and drugs, gastroesophageal reflux disease.

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There were revealed an association of sporadic IPF with allelic variants of the genes *AKAP13, ATP11A, DPP9, DSP, IVD, IL1RN, FAM13A, MUC5B, SFTPC, SPPL2C, TERC, TERT, TOLLIP*. Syndromal IPF develops in German-Pudlak syndrome. Familial cases of the disease are caused by mutations in the genes encoding surfactant (*SFTPC*), mucin (*MUC5B*), deadenylation nuclease (PARN), components of telomere functioning (*RTEL1, TERC, TERT*). In 2000, the American Thoracic Society recommended glucocorticoids and cytostatics for the treatment of ELISA in order to influence the inflammatory process due to the activation of fibroblasts and their accumulation in the extracellular matrix of the lungs. These recommendations are still used by many doctors, despite the publication of reliable data on the increased mortality and hospitalizations of IPF patients taking prednisolone and azathioprine. According to recent meta-analyzes, pirfenidone (an inhibitor of the synthesis of procollagen I and II growth factors) and nintenadib (a tyrosine kinase inhibitor) are the most effective treatments for IPF. Since genetic factors play an important role in the etiopathogenesis of the disease, it is promising to search for methods of targeted therapy for IPF using specific noncoding RNAs as targets, changes in the expression of which are not specific of other bronchopulmonary diseases. These RNAs include miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (decreased expression in IPF); miR-340, miR-424, miR-487b, miR-493, lncRNA AP003419.16, lncRNA AP003419.16 (increased expression in IPF).

Key words: *diagnosis, idiopathic pulmonary fibrosis, treatment, developmental mechanism, microRNA, heredity*

Conflict of interests

The authors declare no conflict of interests

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ATS — American Thoracic Society, CT — computed tomography, EGCG — epigallocatechin gallate, ERS — European Respiratory Society, GWAS — genome-wide association study, IPF — idiopathic pulmonary fibrosis, ncRNA — non-coding RNA, PRM — pulmonary rehabilitation mixture, TGF-β — transforming growth factor beta, ThO — thoracic organs, VC — vital capacity

List of genes with decoding:

AKAP13 — A-kinase anchor protein 13

AP3B1 — adaptor related protein complex 3 subunit beta 1; gene of the protein of AP-3 heterodimer complex that interacts with the scaffold protein clathrin

ATP11A — sodium/potassium/transporting ATPase subunit alpha-1; gene of the alpha-1 ATPase subunit that transports sodium and potassium

DPP9 — dipeptidyl peptidase 9; gene encoding a serine protease of the S9B family

DSP — desmoplakin gene

IVD — isovaleryl-CoA dehydrogenase

IL1RN — interleukin 1 receptor antagonist

FAM13A — family with sequence similarity 13 member A; small GTPase-mediated signal transduction regulation gene

KANSL1 — KAT8 regulatory NSL complex subunit 1; subunit gene of two protein complexes (MLL1 and NSL1) involved in histone acetylation

MUC5B — mucin 5B

PARN — poly(A)-specific ribonuclease; deadenylation nuclease gene

RTEL1 — regulator of telomere elongation helicase 1; gene encoding telomere elongation helicase

SFTPC — surfactant protein C; gene encoding surfactant proteins

SPPL2C — signal peptidase like 2C; gene encoding a protein involved in the proteolysis of membrane proteins

TERC — telomerase RNA component; gene involved in the functioning of telomeres

TERT — telomerase reverse transcriptase; gene encoding telomere reverse transcriptase

TOLLIP — toll interacting protein; gene for a ubiquitin-binding protein that interacts with Toll-like receptors

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe progressive interstitial lung disease with average prevalence of 15:100,000 individuals worldwide [1]. Based on etiology, this disease can be classified into familial, syndromic and sporadic types. About 10–15 % of all IPF cases are familial [2]. They are caused by mutations in genes *SFTPC* [3], *TERC* [4], *TERT* [5], *MUC5B* [6], *RTEL1, PARN* [7]. Syndromic IPF can develop in Hermansky — Pudlak syndrome (mutation in gene *AP3B1*) [8]. Age-associated sporadic cases of IPF are prevailing. Average age of patients with these types is 66, and the risk of disease development in people 75+ increases 50-fold compared with the age group 18–34 [9]. Further, IPF is associated with viral infections (Epstein–Barr virus, cytomegalovirus, herpesviruses [10], Kaposi's sarcoma, and hepatitis C), as well as with smoking and inhalation of metal [11], silicon, beryllium and coal dust; exposure to asbestos, radiation, drugs such as antibiotics (nitrofurantoin, ethambutol), cytostatics (bleomycin, methotrexate), non-steroidal anti-inflammatory drugs [2]; gastroesophageal reflux disease [12]. The aforementioned environmental factors cause chronic damage to alveolar epithelium that contributes to the development

of immune response with the release of transforming growth factor β (TGF-β) that is a profibrotic cytokine activating angiogenesis and the production of extracellular matrix components (collagen and fibronectin) [2]. Fig. 1 is a schematic presentation of mechanisms of the development of different IPF types.

To diagnose IPF, a clinician should consider the specific features of the clinical presentation of disease, the results of X-ray examinations, and physiological parameters of patients. Surgical lung biopsy (open thoracotomy or videothoracoscopy) is recommended for most patients with IPF. The main objective of subsequent histological examination is to confirm the diagnosis of IPF [13]. Basic clinical signs of IPF include dyspnea (in 88 % of patients), dry cough (70 %), and chest pain (24 %) [5]. In 2000, the American Thoracic Society established major and minor criteria for IPF. Major criteria include the following: 1) absence of other known causes of idiopathic lung diseases, such as exposure to toxic drugs and environmental factors, connective tissue diseases; 2) decreased vital capacity (VC), often along with increased forced expiratory volume/VC ratio, signs of impaired gas exchange; 3) bibasilar reticular anomalies with minimal ground-glass opacities found during the computed tomography (CT) of thoracic organs (ThO); 4) absence of the signs of an alternative diagnosis based on the results of transbronchial lung biopsy or bronchoalveolar lavage. Minor criteria are listed below: 1) age 50+; 2) latent onset of unexplained dyspnea during physical exertion; 3) disease duration more than 3 months; 4) bibasilar rales on suspended deep inspiration (dry or velcro-type) [13]. ThO CT results with subpleural honeycombing and traction bronchiectasis (Fig. 2) or specific combinations of X-ray and histological signs in patients after surgical lung biopsy are essential for the diagnosis [11].

Since an important mechanism for IPF development is inflammation that leads to the activation of fibroblasts and their accumulation in extracellular matrix, in 2000, American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommended administration of glucocorticoids (prednisolone at a dose of 0.5 mg per kg body weight per day), azathioprine (2–3 mg/kg body weight) or cyclophosphamide (2 mg/kg body weight) for the management of this disease [13]. Unfortunately, these recommendations are still used by practitioners, although in 2012 there was evidence of the ineffectiveness of this treatment. Moreover, patients with IPF receiving the combination of prednisolone, azathioprine, and N-acetylcysteine

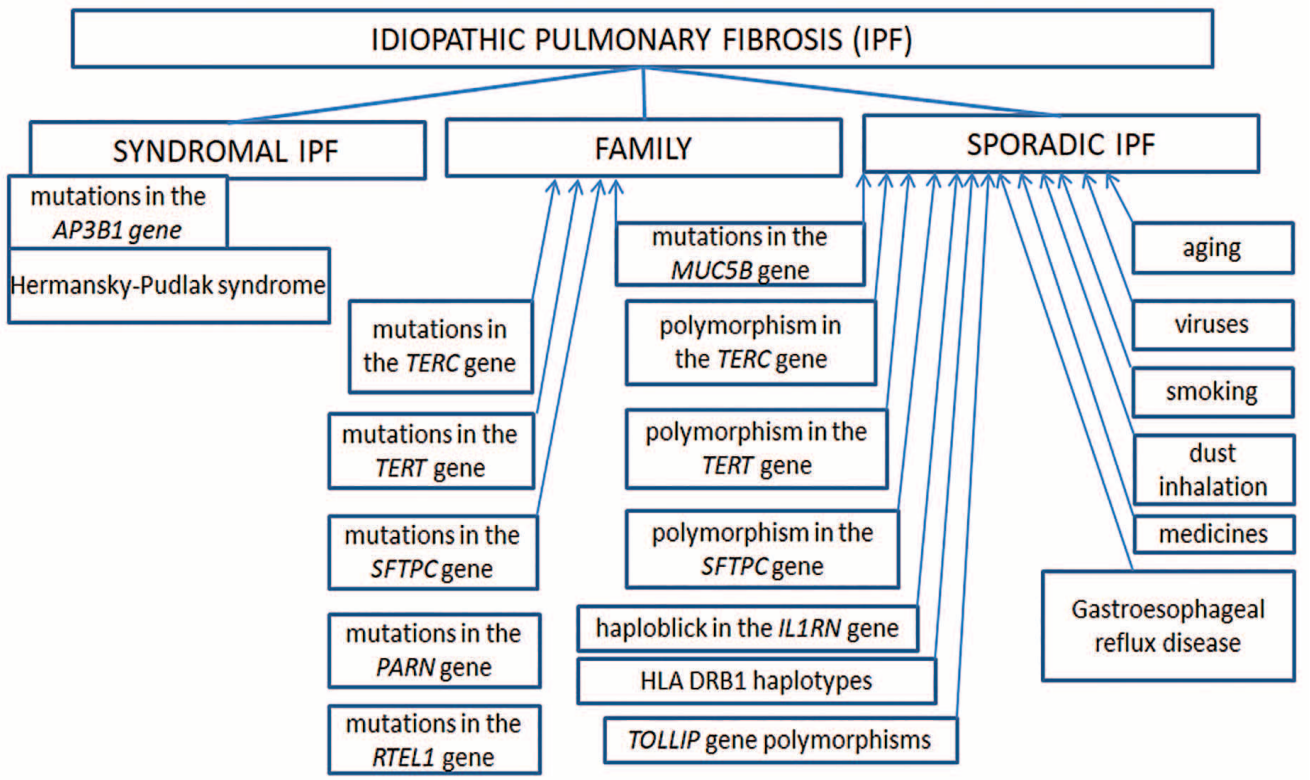

Figure 1. *Scheme of pathogenetically significant mechanisms of IPF* [1]

[1] AP3B1 gene — Adaptor Related Protein Complex 3 Subunit Beta 1; TERC gene — Telomerase RNA Component; TERT gene — Telomerase Reverse Transcriptase; SFPC gene — Surfactant Protein C; PARN gene — Poly(A)-Specific Ribonuclease; RTEL gene — Regulator of Telomere Elongation Helicase 1; MUC5B gene — Mucin 5B; IL1RN gene — Interleukin 1 Receptor Antagonist; HLA DRB1 — Human Leukocyte Antigens DR beta chain; TOLLIP gene — Toll Interacting Protein

had an increased risk of mortality and hospitalization [14]. Despite ongoing treatment, survival rate in cases of IPF is about 3 years [15]. Therefore, analysis of the molecular mechanisms of IPF development can become the basis for new effective treatment methods. Thus, one of the approaches is to activate the expression of sirtuin (histone acetylase) SIRT7 that reduces collagen production by lung fibroblasts. SIRT7 levels are reduced in lung tissues of IPF patients and experimental mice with bleomycin-induced IPF [15]. Since up to 15 % of all cases of this disease are monogenic [2], that is, they are caused by mutations in a specific gene, consideration of the mechanisms of their development can become the basis for the development of a pathogenetic therapy for patients with IPF.

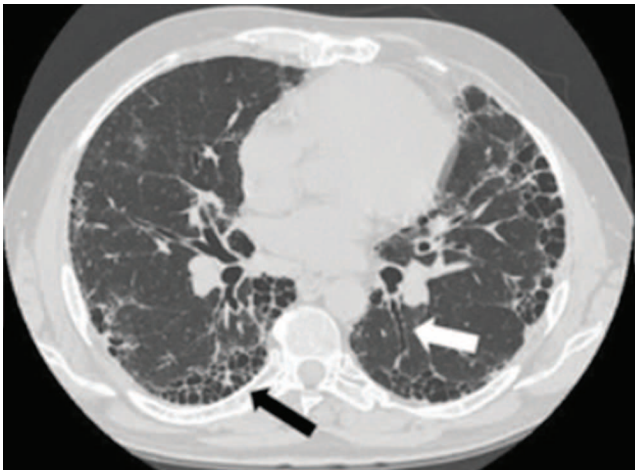

Figure 2. *Typical manifestations of IPF on CT sections of the chest (the black arrow shows the «honeycomb lung», the white arrow shows traction bronchiectasis) [11]*

According to ThO CT, differential diagnosis of IPF should be carried out with pulmonary signs of systemic scleroderma and rheumatoid arthritis, asbestosis and sarcoidosis. These diseases have signs that are generally similar to those of IPF on CT. However, asbestosis is characterized by the presence of parenchymal strands of fibrosis and pleural plaques. Laboratory blood test is required to exclude systemic connective tissue diseases. Similar to IPF ThO CT with reticular opacities and honeycombing is observed in subacute and chronic hypersensitivity pneumonitis, however, there is no typical for IPF bibasilar predominance [13]. It should be mentioned that risk factors for IPF development are the causes of the development of lung diseases (Fig. 3) that were listed in differential diagnosis [2, 11].

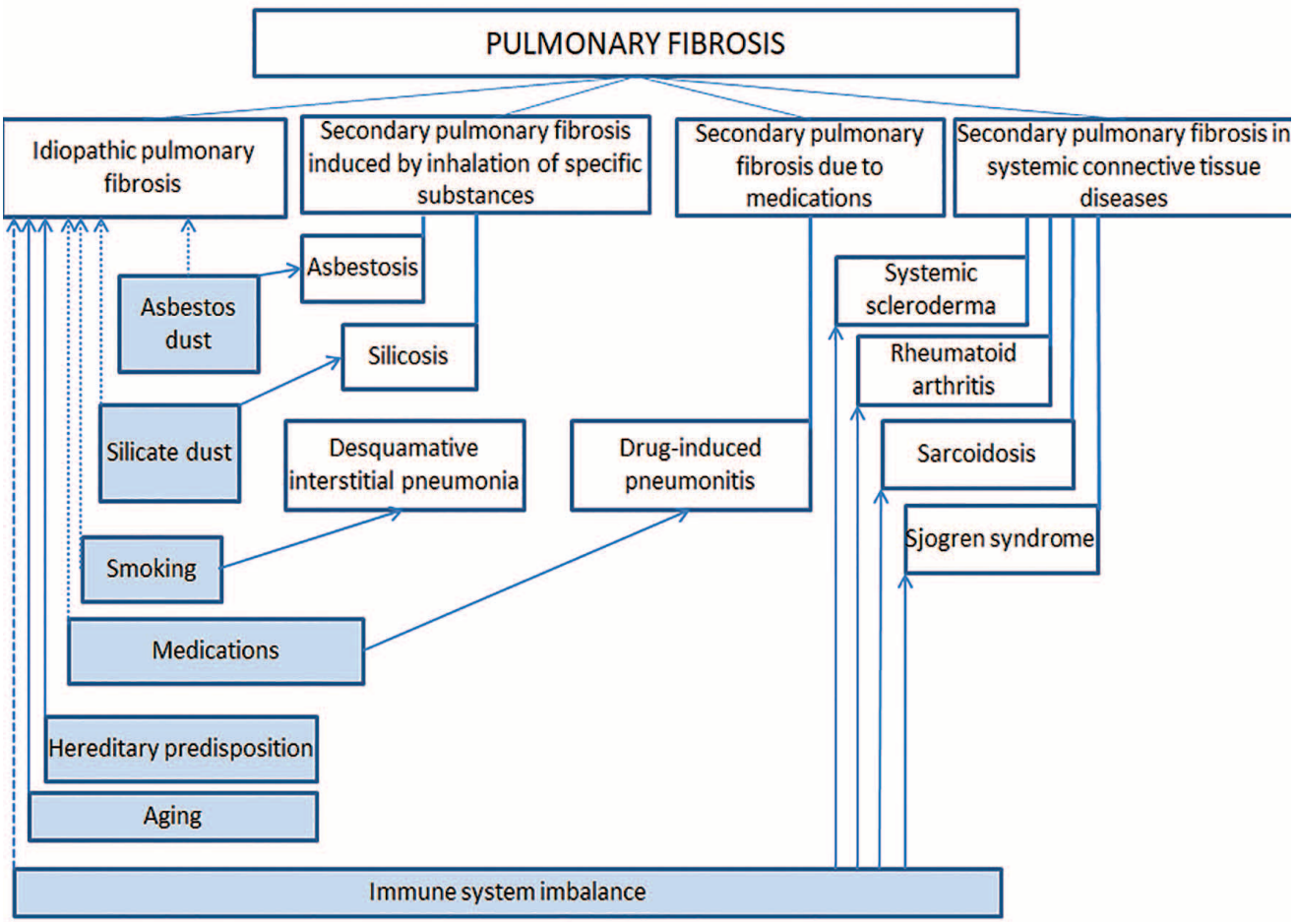

Figure 3. *Scheme of differential diagnosis of IPF with the definition of common causes of disease development*

Familial types of idiopathic pulmonary fibrosis

Clinical signs of monogenic cases of IPF caused by mutations in specific genes are characterized by earlier manifestation [16], autosomal dominant inheritance, and varying penetrance. These types of IPF were described as early as 1958 [17]. Mutations are most often (18 % of all family cases) detected in the genes encoding telomerase complex: *TERT* (c.97C>T, c.430G>A, c.1456C>T, c.2240delT, c.2593C>T, c.2594G>A, c.3346_3522del [4]; c.1892G>A, c. 2594G>A, c.2648T>G [5]) and *TERC* (r.37a>g) [4]. Major missense mutation 128T>A in exon 5 of the gene *SFTPC* (encodes surfactant) is typical [3]. Rarer mutations are c.602delG, c.1451C>T, c.1940C>T, c.2005C>T, c.3371A>C in the gene *RTEL1* that encodes a helicase that regulates telomere elongation, as well as IVS4-2a>g, c.529C>T, c563_564insT, c.751delA, IVS16+1g>a, c.1262A>G mutations in the gene *PARN* that encodes deadenylation nuclease [7].

It should be mentioned that sporadic cases of IPF may be associated with allelic variants of genes with mutations that cause familial IPF. Thus, there's a description of association rs12696304 in the gene *TERC,* rs7725218 in the gene *TERT* [18], polymorphisms G4702C, C4859G, G4877A, G5089A, C5210A, G5236A, G5574A, A5786C, T6108C, C6699T in the surfactant gene *SFTPC* [16] with the development of sporadic IPF. Allelic variant rs35705950 (nucleotide substitution in the promoter region) in the gene *MUC5B* (encodes mucin) was reported as a cause of both familial [6] and sporadic cases of IPF [18–20]. The significance of mutations in genes *TERT* [4, 5], *TERC* [4], *RTEL1* [7] in the development of monogenic IPF forms, as well as the association of sporadic forms of the disease with allelic variants of genes *TERT* and *TERC* [18], whose expression products are necessary for the functioning of telomeres, explains the association of IPF with aging. Genomic instability, mitochondrial dysfunction, cellular aging, and loss of proteostasis are actually mentioned in the pathogenesis of this disease [21].

According to the results of meta-analyzes, allelic variants of many other IPF-associated genes were found that are not monogenic types of this disease. Many of the products of these genes may be involved in IPF pathogenesis. For example, VNTR*2 haploblock in the interleukin receptor gene *IL1RN* was significantly associated in 5 different clinical trials indicating pathological inflammatory reactions [22]. Information on the association of haplotypes *DRB1*15:01* and *DQB1*06:02* of major histocompatibility complex genes *HLA* is illustrative of the role of autoimmune processes [23]. The association of allelic variants of the gene *TOLLIP* was also identified; this gene encodes a Toll-interacting protein involved in the innate immune system function (variants rs111521887, rs5743894, rs5743890) [19]. According to the results of the genome-wide association study (GWAS), IPF was associated with allelic variants of genes, the role of protein products of which was not yet determined. These include the gene of serine protease *DPP9* (rs12610495), lymphoblastic oncogene *AKAP13* (rs62023891), desmoplakin for intercellular contacts *DSP* (rs2076295), component of histone acetylation complex *KANSL1*, membrane ATPase that regulates the transport of calcium ions *ATP11A* (rs9577395), isovaleryl-CoA dehydrogenase *IVD* (rs59424629), hypoxia-induced gene associated with lung cancer *FAM13A* (rs2013701) [18], lysosomal membrane protein with a conserved transmembrane domain *SPPL2C* (rs17690703) [19]. Analysis of the role of specific genes in IPF development can become the basis for the development of both criteria for accurate diagnosis and management of this disease.

Present-day methods of management of idiopathic pulmonary fibrosis

Considering the key role of fibroblasts in the pathogenesis of IPF [15], use of antifibrotic agents for the management of this disease seems to be the most promising way. A 2016 meta-analysis of the results of treatment of 2,254 patients with IPF demonstrated significant effectiveness of pirfenidone (an inhibitor of the synthesis of procollagen growth factors I and II) and nintenadib (a tyrosine kinase inhibitor) in improving reduced FVC (forced vital capacity) during 12 months. The inefficiency of N-acetylcysteine and the development of several adverse drug reactions during its administration were found [24]. Similar results were obtained in a 2021 meta-analysis that revealed greater efficacy of pamrevlumab (a human monoclonal antibody that inhibits the activity of connective tissue growth factor). However, only pirfenidone was able to reduce overall mortality [25]. It should be mentioned that nintedanib that is also effective in the management of lung cancer affects the same pathways, including MAPK, PI3K/AKT, JAK/STAT, TGF-β, VEGF, Wnt [26] that involve miRNA (ribonucleic acid) associated with IPF [27]. In addition to antifibrotic agents, present-day treatment for IPF includes proton pump inhibitors, oxygen therapy, and lung transplantation. In some cases, the effectiveness of antibacterial and antiviral agents was demonstrated due to the role of bacteria and viruses in the development of IPF. It was found, for example, that macrolides have immunomodulatory and anti-inflammatory effect in IPF preventing the production of mediators of the immune system [2].

In addition to medications, the possibility of using traditional medicine for IPF management is also being considered. A Chinese herbal pulmonary rehabilitation mixture (PRM) that has been used for decades was proposed as a potential multipurpose oral agent for IPF management. Pharmacodynamic studies have shown that PRM affects the state of the epithelium, endothelium, fibroblasts, platelet growth factor, toll-like receptor-4, and fibroblast growth factor. PRM contains 8 herbs: roots of astragalus, codonopsis, ophiopogon, pseudoginseng, anemarrhena, licorice, bulbs of Fritillaria thunbergii, fruits of Schisandra chinensis [1]. Components of *Hypericum longistylum* demonstrated effect on TGF-β1/Smad3 signaling pathways which indicates their potential use for IPF management [28]. Epigallocatechin-3-gallate (EGCG) that is found in green tea inhibits the aggregation of pathological structures of SP-A2 by increasing the instability of this protein and activating its proteasomal degradation. Therefore, EGCG can be an agent in the management of IPF [29].

Since genetic factors are central to the development of this disease, finding ways to impact these IPF development mechanisms is an important task. Investigation of the role of epigenetic factors is the most promising trend of studies, since these factors are reversible and can be corrected using non-coding RNAs (ncRNAs) that are the potential targets as well. One example is microRNA miR-506 that specifically binds to the RNA of the p65 NF-κB subunit gene (nuclear transcription factor for apoptosis, cell cycle, and immune response genes) and suppresses its expression. In IPF, level of this miRNA is significantly reduced; therefore, miR-506 can be used to inhibit excessive cell proliferation and inflammation in lung tissues [30]. Back in 2010, the efficacy of antisense miR-21 in mice with bleomycin-induced lung fibrosis was described. The effect of these molecules could also be due to the suppression of proliferation, since increased expression of miR-21 is typical for malignant neoplasms, and in IPF it contributes to the pathological activation of fibroblasts that synthesize this miRNA. MiR-21 regulates the expression of Smad7 by influencing TGF-β1 that contributes to the hyperproduction of extracellular matrix [31].

An inverse correlation of miR-708-3p expression with the development of pulmonary fibrosis was found what indicates the potential use of this miRNA in the management of IPF. Direct targets for miR-708 include transcripts of the genes of disintegrin and metalloproteinase 17 (*ADAM17*). In an animal experiment, the therapeutic efficacy of this microRNA in pulmonary fibrosis was demonstrated [32]. MiR-184 also has an antifibrotic effect that suppresses TGFβ-induced fibrotic processes in lungs and can be considered for the targeted therapy of IPF [33]. In addition to miRNAs, long ncRNAs can be used in the management of IPF. Although the results of clinical trials have revealed decreased expression of 1,376 and increased expression of 440 different long ncRNAs in the blood plasma of IPF patients compared with healthy individuals, changes in the levels of certain ones is more specific. These include lncRNA AP003419.16 that is expressed at the highest level and activates TGF-β1 signaling pathways [34]. An interfering sequence for profibrotic lncITPF (involved in TGFβ pathways) has already been used in clinical practice in patients with IPF. This agent called sh-lncITPF actually reduced lung fibrosis score [35]. Antifibrotic lncRNA PCAT29 (prostate cancer-associated transcript 29) suppresses TGF-β and can be used to influence the TGF-β pathway in IPF [36]. Thus, studies of ncRNAs in the development of IPF can become the basis for both diagnosis and the development of more effective methods of treatment (Fig. 4).

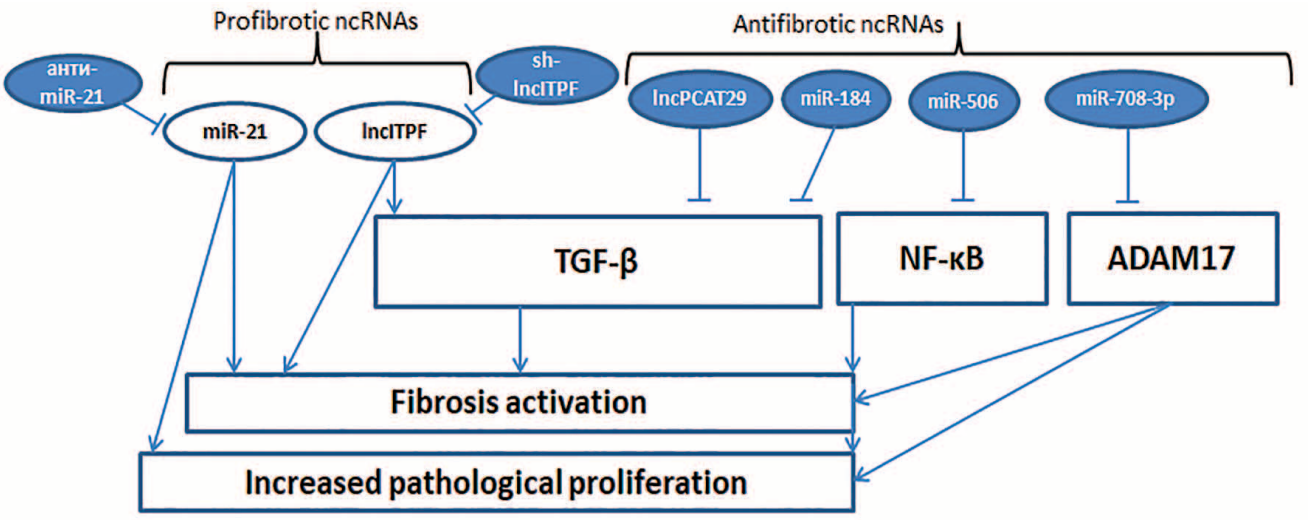

Figure 4. *Scheme for the use of specific non-coding RNAs (ncRNAs) in the treatment of idiopathic pulmonary fibrosis*

Table 1. *IPF-specific miRNAs*

miRNAs (gene localization)	Expression changes specificity in IPF/ mechanism of influence	Reference
miR-9-5p (5q14.3)	decreases / prevents fibrosis	[38]
miR-27b (9q22.32)		
miR-153 (2q35)	decreases / suppresses TGF-β	
miR-184 (15q25.1)	decreases / suppresses TGF-β and p53	[33]
miR-326 (11q13.4)	decreases / prevents fibrosis	[38]
miR-340 (5q35.3)	increases / affects MAPK signaling	[41]
miR-374 (Xq13.2)	decreases / suppresses mTOR signaling, expression of MID1 ubiquitin ligase	[27, 42]
miR-424 (Xq26.3)	increases / stimulates fibrosis	[38]
miR-487b (14q32.31)	increases / suppresses IL-33 expression	[36, 43]
miR-489 (7q21.3)	decreases / prevents fibrosis	[38]
miR-493 (14q32.2)	increases / inhibits Wnt/B-catenin, Wnt/PCP, MEK/ERK, PI3K/AKT pathways	[43, 44]
miR-630 (15q24.1)	decreases / regulates *CDH2, VIM, EZH2, SOCS2, TFG, TLR4, Smad9, EP300* gene expression	[45]
miR-1343 (11p13)	decreases / inhibits TGF-β receptors	[40]

miRNAs as potential diagnostic markers of idiopathic pulmonary fibrosis

In addition to the miRNAs described above that can be considered as targets for targeted therapy, a significant change in the expression of miR-29, miR-21-5p, miR-92a-3p, miR-26a-5p, and let-7d-5p was found in patients with IPF [37]. Patients with IPF demonstrate changes in the levels of miRNAs that activate TGF-β (miR-424) and suppress its transcription (miR-9-5p, miR-18a-5p, miR-26a, miR-27b, miR-101, miR-153, miR- 326, miR-489, miR-1343) [38]. MiR-323a inhibits both TGF-β and TGF-α signaling pathways. Expression of this miRNA is significantly reduced in the lung tissue of patients with IPF [39]. Fibroblasts in the lung tissue of patients with IPF express lower levels of miR-101 [40]. In patients with IPF have altered levels of many specific microRNAs that may be involved in the pathogenesis of this disease compared with healthy ~~control~~ individuals. 47 microRNAs were identified that are involved in the regulation of actin cytoskeleton, in signaling pathways TGF-β, Wnt, PI3K-Akt, Notch, HIF-1, and mitogen-activated protein kinase [27]. Analysis of literature sources presented in PubMed, Scopus, Web of Science databases revealed that changes in the expression of many IPF-associated microRNAs are also found in patients with other diseases of bronchopulmonary system, such as asthma and chronic obstructive pulmonary disease. However, the expression of several microRNAs is detected only in IPF (Table 1). These miRNAs can be used as diagnostic markers of this disease, as well as for the development of effective targeted therapy.

Conclusion

Average incidence of IPF is 1:6,500. From 10 to 15 % of cases of this disease are autosomal dominant monogenic diseases caused by mutations in the genes of telomerase complex (*TERC, TERT, RTEL*), surfactant (*SFTPC*), deadenylating nucleases (*PARN*) and mucin (*MUC5B*). Sporadic cases of IPF are associated with allelic variants of different genes, the products of which may be involved in the pathogenesis of this disease. The ineffectiveness of IPF management with glucocorticoids and cytostatics has been proven; these agents can aggravate disease course and increase the risk of mortality. Present-day effective methods of treatment implemented in clinical practice are the use of pirfenidone (an inhibitor of the synthesis of procollagen growth factor), nintenadib (a tyrosine kinase inhibitor) and pamrevlumab (an anti-connective tissue growth factor monoclonal antibody). Promising method of laboratory tests for IPF is determining the levels of miRNAs, changes in the expression of which is specific only for this disease. These include miR-9-5p, miR-27b, miR-153, miR-184, miR-326, miR-374, miR-489, miR-630, miR-1343 (decreasing levels); miR-340, miR-424, miR-487b, miR-493 (increasing level). MicroRNAs and long non-coding RNAs can also be used in the development of targeted therapy for IPF.

Список литературы/Reference:

1. Zhao J., Ren Y., Qu Y. et al. Pharmacodynamic and pharmacokinetic assessment of pulmonary rehabilitation mixture for the treatment of pulmonary fibrosis. Sci. Rep. 2017; 7: 3458. doi: 10.1038/s41598-017-02774-1.

2. Chioma O.S., Drake W.P. Role of Microbial Agents in Pulmonary Fibrosis. Yale J. Biol. Med. 2017; 90: 219-227.
3. Thomas A.Q., Lane K., Phillips J. et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am. J. Respir. Crit. Care. Med. 2002. 1; 165(9): 1322-8. doi: 10.1164/rccm.200112-123OC.
4. Tsakiri K.D., Cronkhite J.T., Kuan P.J. et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc. Natl. Acad. Sci. U S A. 2007; 104(18): 7552-7. doi: 10.1073/pnas.0701009104.
5. Fernandez B.A., Fox G., Bhatia R. et al. A Newfoundland cohort of familial and sporadic idiopathic pulmonary fibrosis patients: clinical and genetic features. Respir. Res. 2012; 13:64. doi: 10.1186/1465-9921-13-64.
6. Seibold M.A., Wise A., Speer M. et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N. Engl. J. Med. 2011; 364: 1503–12. doi: 10.1056/NEJMoa1013660.
7. Stuart B.D., Choi J., Zaidi S. et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat. Genet. 2015; 47: 512–517. doi: 10.1038/ng.3278.
8. Gochuico B.R., Huizing M., Golas G.A. et al. Interstitial lung disease and pulmonary fibrosis in Hermansky-Pudlak syndrome type 2, an adaptor protein-3 complex disease. Mol. Med. 2012; 18(1): 56-64. doi: 10.2119/molmed.2011.00198.
9. Raghu G., Weycker D., Edelsberg J. et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care. Med. 2006; 174: 810-816. doi: 10.1164/rccm.200602-163OC.
10. Sheng G., Chen P., Wei Y. et al. Viral Infection Increases the Risk of Idiopathic Pulmonary Fibrosis: A Meta-Analysis. Chest. 2020; 157(5): 1175-1187. doi: 10.1016/j.chest.2019.10.032.
11. Sgalla G., Iovene B., Clavello M. et al. Idiopathic pulmonary fibrosis: pathogenesis and management. Respir. Res. 2018; 19(1): 32. doi: 10.1186/s12931-018-0730-2.
12. Methot D.B., Leblanc E., Lacasse Y. Meta-analysis of Gastroesophageal Reflux Disease and Idiopathic Pulmonary Fibrosis. Chest. 2019; 155: 33-43. doi: 10.1016/j.chest.2018.07.038.
13. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am. J. Respir. Crit. Care. Med. 2000; 161: 646-64. doi: 10.1164/ajrccm.161.2.ats3-00.
14. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G., Anstrom K. et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N. Engl. J. Med. 2012; 366(21): 1968-77. doi: 10.1056/NEJMoa1113354.
15. Wyman A.E., Noor Z., Fishelevich R. et al. Sirtuin 7 is decreased in pulmonary fibrosis and regulates the fibrotic phenotype of lung fibroblasts. Am. J. Physiol. Lung. Cell. Mol. Physiol. 2017; 312: L945-L958. doi: 10.1152/ajplung.00473.2016.
16. Lawson W.E., Grant S.W., Ambrosini V. et al. Genetic mutations in surfactant protein C are a rare cause of sporadic cases of IPF. Thorx. 2004; 59(11): 977-80. doi: 10.1136/thx.2004.026336.
17. McKusick V.A., Fisher A.M. Congential cystic disease of the lung with progressive pulmonary fibrosis and carcinomatosis. Ann. Intern. Med. 1958; 48: 774-90. doi: 10.7326/0003-4819-48-4-774.
18. Allen R.J., Guillen-Guio B., Oldham J.M. et al. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis. Am. J. Respir. Crit. Care. Med. 2020; 201(5): 564-574. doi: 10.1164/rccm.201905-1017OC.
19. Noth I., Zhang Y., Ma S.F. et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. Lancet Respir Med. 2013; 1(4): 309-317. doi: 10.1016/S2213-2600(13)70045-6.
20. Lee M.G., Lee Y.H. A meta-analysis examining the association between the MUC5B rs35705950 T/G polymorphism and susceptibility to idiopathic pulmonary fibrosis. Inflamm. Res. 2015; 64(6): 463-70. doi: 10.1007/s00011-015-0829-6.
21. Gulati S., Thannickal V.J. The Aging Lung and Idiopathic Pulmonary Fibrosis. Am. J. Med. Sci. 2019; 357: 384-389. doi: 10.1016/j.amjms.2019.02.008. doi: 10.1016/j.amjms.2019.02.008.
22. Korthagen N.M., van Moorsel C.H., Kazemier K.M. et al. IL1RN genetic variations and risk of IPF: a meta-analysis and mRNA expression study. Immunogenetics. 2012; 64: 371-377. doi: 10.1007/s00251-012-0604-6.
23. Fingerlin T.E., Zhang W., Yang I.V. et al. Genome-wide imputation study identifies novel HLA locus for pulmonary fibrosis and potential role for auto-immunity in fibrotic idiopathic interstitial pneumonia. BMC Genet. 2016; 17(1): 74. doi: 10.1186/s12863-016-0377-2.
24. Rogliani P., Calzetta L., Cavalli F. et al. Pirfenidone, ninitedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulm. Pharmacol. Ther. 2016; 40: 95-103. doi: 10.1016/j.pupt.2016.07.009.
25. Martino E.D., Provenzani A., Vitulo P. et al. Systematic Review and Meta-analysis of Pirfenidone, Niniedanib, and Pamrevlumab for the Treatment of Idiopathic Pulmonary Fibrosis. Ann. Pharmacother. 2021; 55(6): 723-731. doi: 10.1177/1060028020964451.
26. Landi C., Carleo A., Vantaggiato L. et al. Common molecular pathways targeted by nintdanib in cancer and IPF: A bioinformatic study. Pulm. Pharmacol. Ther. 2020; 64: 101941. doi: 10.1016/j.pupt.2020.101941.
27. Yang G., Yang L., Wang W. et al. Discovery and validation of extracellular/ circulating microRNAs during idiopathic pulmonary fibrosis disease progression. Gene. 2015; 562: 138-44. doi: 10.1016/j.gene.2015.02.065.
28. Li X., Liu S., Zhai Y. et al. In vitro screening for compounds from Hypericum longistylum with anti-pulmonary fibrosis activity. Bioorg. Med. Chem. Lett. 2019; 29: 126695. doi: 10.1016/j.bmcl.2019.126695.
29. Quan Y., Li L., Dong L. et al. Epigallocatechin-3-gallate (EGCG) inhibits aggregation of pulmonary fibrosis associated mutant surfactant protein A2 via a proteasomal degradation pathway. Int. J. Biochem. Cel. Biol. 2019; 116: 105612. doi: 10.1016/j.biocel.2019.105612.
30. Zhu M., An Y., Zhang X. et al. Experimental pulmonary fibrosis was suppressed by microRNA-506 through NF-kappa-mediated apoptosis and inflammation. Cell. Tissue Res. 2019; 378: 255-265. doi: 10.1007/s00441-019-03054-2.
31. Liu G., Friggeri A., Yang Y. et al. miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. J. Exp. Med. 2010; 207(8): 1589-97. doi: 10.1084/jem.20100035.

32. Liu B., Li R., Zhang J. et al. MicroRNA-708-3p as a potential therapeutic target via the ADAM17-GATA/STAT3 axis in idiopathic pulmonary fibrosis. Exp. Mol. Med. 2018; 50(3): e465. doi: 10.1038/emm.2017.311.
33. Li J., Pan C., Tang C. et al. miR-184 targets TP63 to block idiopathic pulmonary fibrosis by inhibiting proliferation and epithelial-mesenchymal transition of airway epithelial cells. Lab Invest. 2021; 101(2): 142-154. doi: 10.1038/s41374-020-00487-0.
34. Hao X., Du Y., Qian L. et al. Upregulation of long noncoding RNA AP003419.16 predicts high risk of aging-associated idiopathic pulmonary fibrosis. Mol. Med. Rep. 2017; 16(6): 8085-8091. doi: 10.3892/mmr.2017.7607.
35. Song X., Xu P., Meng C. et al. LncITPF Promotes Pulmonary Fibrosis by Targeting hnRNP-L Depending on Its Host Gene ITGBL1. Mol. Ther. 2019;27(2):380-93. doi: 10.1016/j.ymthe.2018.08.026.
36. Liu H.C., Liao Y., Liu C.Q. miR-487b mitigates allergic rhinitis through inhibition of the IL-33/ST2 signaling pathway. Eur. Rev. Med. Pharmacol. Sci. 2018; 22(23): 8076-8083. doi: 10.26355/eurrev_201812_16497.
37. Bagnato G., Roberts W.N., Roman J., Gangemi S. A systematic review of overlapping microRNA patterns in systemic sclerosis and idiopathic pulmonary fibrosis. Eur. Respir. Rev. 2017; 26: pii: 160125. doi: 10.1183/16000617.0125-2016.
38. Kang H. Role of MicroRNAs in TGF-β Signaling Pathway-Mediated Pulmonary Fibrosis. Int. J. Mol. Sci. 2017; 18: pii: E2527. doi: 10.3390/ijms18122527.
39. Ge L., Habiel D.M., Hansbro P.M. et al. miR-323a-3p regulates lung fibrosis by targeting multiple profibrotic pathways. JCI Insight. 2016; 1(20): e90301. doi: 10.1172/jci.insight.90301.
40. Huang C., Xiao X., Yang Y. et al. MicroRNA-101 attenuates pulmonary fibrosis by inhibiting fibroblast proliferation and activation. J. Biol. Chem. 2017; 292: 16420-16439. doi: 10.1074/jbc.M117.805747.
41. Wei Y.Q., Guo Y.F., Yang S.M. et al. MiR-340-5p mitigates the proliferation and activation of fibroblast in lung fibrosis by targeting TGF-β/p38/ATF1 signaling pathway. Eur. Rev. Med. Pharmacol. Sci. 2020; 24(11): 6252-61. doi: 10.26355/eurrev_202006_21523.
42. Unterbruner K., Matthes F., Schilling J. et al. MicroRNAs miR-19, miR-340, miR-374 and miR-542 regulate MID1 protein expression. PLoS One. 2018; 13(1): e0190437. doi: 10.1371/journal.pone.0190437.
43. Zhang Y.F., Gu L.N., Qi J. et al. Construciton of potential idiopathic pulmonary fibrosis related microRNA and messenger RNA regulatory network. Chin. Med. J. (Engl). 2021; 134(5): 584-86. doi: 10.1097/CM9.0000000000001276.
44. Huang L., Huang L., Li Z., Wei Q. Molecular Mechainsims and Therapeutic Potential of miR-493 in Cancer. Crit. Rev. Eukaryot. Gene Expr. 2019; 29(6): 521-528. doi: 10.1615/CritRevEukaryotGeneExpr.2019030056.
45. Li R., Wang Y., Song X. et al. Potential regulatory role of circular RNA in idiopathic pulmonary fibrosis. Int. J. Mol. Med. 2018; 42: 3256-68. doi: 10.3892/ijmm.2018.3892.