DOI: 10.20514/2226-6704-2024-14-6-405-418
УДК 616.24-002.155-056.43-07-085
EDN: LYHBFO

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ИДИОПАТИЧЕСКИЙ ЛЕГОЧНЫЙ ФИБРОЗ И ГИПЕРСЕНСИТИВНЫЙ ПНЕВМОНИТ: НОВЫЙ ВЗГЛЯД НА РОЛЬ ГЕНЕТИЧЕСКИХ И ЭПИГЕНЕТИЧЕСКИХ ФАКТОРОВ В РАЗВИТИИ И ТЕЧЕНИИ ЗАБОЛЕВАНИЙ

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Idiopathic Pulmonary Fibrosis and Hypersensitive Pneumonitis: A Fresh View on The Role of Genetic and Epigenetic Factors in The Development and Course of Diseases

Резюме

Учитывая повсеместно прогрессирующий характер и неблагоприятный прогноз, интерстициальные заболевания легких (ИЗЛ), особенно такие часто встречающиеся варианты, как идиопатический легочный фиброз (ИЛФ) и гиперсенситивный пневмонит (ГП), оправданно привлекают значительное внимание клиницистов и ученых по всему миру. В последние годы все большую актуальность приобретает необходимость углубленного изучения клинических и патогенетических особенностей ИЗЛ, совершенствование существующих и разработка новых эффективных персонализированных подходов тактики ведения этой категории пациентов, на основе наиболее перспективных мишеней воздействия, среди которых все более активно рассматриваются генетические и эпигенетические варианты. Авторами проведен нарративный, описательный обзор литературы, направленный на систематизацию данных об основных известных генетических и эпигенетических механизмах, вовлеченных в патогенез и формирование специфических клинических проявлений ИЛФ и ГП. Отдельно выделены мутации в генах, кодирующих теломеразы, синтез факторов фиброгенеза, полиморфизмы генов муцина, сурфактанта легких, основные эпигенетические изменения, вовлеченные в процессы фиброгенеза. Проанализированы перспективы генетических и эпигенетических исследований для новых фармакологических подходов и мониторинга эффекта уже доступных методов лечения. Поиск литературных источников проводился по базам данных Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka и РИНЦ, по ключевым словам, «интерстициальные заболевания легких», «идиопатический легочный фиброз», «гиперсен-

ситивный пневмонит», «семейный легочный фиброз», «генетический», «эпигенетический», «прецизионная диагностика», «терапия» с глубиной поиска 20 лет.

Ключевые слова: *интерстициальные заболевания легких, идиопатический легочный фиброз, гиперсенситивный пневмонит, семейный легочный фиброз, генетический, эпигенетический, MUC5B, TERT, теломеры, сурфактант, терапия*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.08.2024 г.
Одобрена рецензентом 23.09.2024 г.
Принята к публикации 14.10.2024 г.

Для цитирования: Архангельская Е.Е., Лямина С.В., Кожевникова Е.О. и др. ИДИОПАТИЧЕСКИЙ ЛЕГОЧНЫЙ ФИБРОЗ И ГИПЕРСЕНСИТИВНЫЙ ПНЕВМОНИТ: НОВЫЙ ВЗГЛЯД НА РОЛЬ ГЕНЕТИЧЕСКИХ И ЭПИГЕНЕТИЧЕСКИХ ФАКТОРОВ В РАЗВИТИИ И ТЕЧЕНИИ ЗАБОЛЕВАНИЙ. Архивъ внутренней медицины. 2024; 14(6): 405-418. DOI: 10.20514/2226-6704-2024-14-6-405-418. EDN: LYHBFO

Abstract

Given their ubiquitous progressive nature and unfavorable prognosis, interstitial lung diseases (ILD), especially such common variants as idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis (HP), rightly attract considerable attention from clinicians and scientists worldwide. In recent years, the need for an in-depth study of the clinical and pathogenetic features of ILD, improvement of existing approaches and development of effective personalized approaches to the management of this category of patients, based on the most promising targets of action, among which genetic and epigenetic variants are increasingly being considered, has become increasingly important. The authors conducted a non-systematic, descriptive review of the literature aimed at systematizing data on the main known genetic and epigenetic mechanisms involved in the pathogenesis and formation of specific clinical manifestations of IPF and HP. Mutations in genes encoding telomerase, synthesis of fibrogenesis factors, polymorphisms of mucin genes, lung surfactant are highlighted separately, and the main epigenetic changes involved in fibrogenesis processes are highlighted separately. Prospects of genetic and epigenetic studies for new pharmacological approaches and monitoring the effect of already available treatment methods are analyzed. The search for literature sources was conducted in the Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka, and RSCI databases by the keywords "interstitial lung diseases", "idiopathic pulmonary fibrosis", "hypersensitivity pneumonitis", "familial pulmonary fibrosis", "genetic", "epigenetic", "precision diagnostics", "therapy" with a search depth of 20 years.

Key words: *interstitial lung diseases, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, familial pulmonary fibrosis, genetic, epigenetic, MUC5B, TERT, telomeres, surfactant, therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 22.08.2024
Reviewer approved 23.09.2024
Accepted for publication on 14.10.2024

For citation: Arkhangelskaya E.E., Lyamina S.V., Kozhevnikova E.O. et al. Idiopathic Pulmonary Fibrosis and Hypersensitive Pneumonitis: A Fresh View on The Role of Genetic and Epigenetic Factors in The Development and Course of Diseases. The Russian Archives of Internal Medicine. 2024; 14(6): 405-418. DOI: 10.20514/2226-6704-2024-14-6-405-418. EDN: LYHBFO

HSP — hypersensitive pneumonitis, CD — Christian's disease, DIP — desquamative interstitial pneumonia, ILD — interstitial lung disease, IIP — idiopathic interstitial pneumonia, IPF — idiopathic pulmonary fibrosis, COP — cryptogenic organizing pneumonia, LAM — lymphangioleiomyomatosis, LIP — lymphocytic interstitial pneumonia, PF — pulmonary fibrosis, NIP — non-specific interstitial pneumonia, AIP — acute interstitial pneumonia, RB — respiratory bronchitis, ILD RB — interstitial lung disease-associated respiratory bronchitis, SCTD — systemic connective tissue diseases, FPF – family history of idiopathic pulmonary fibrosisa, TNF-α — tumour necrosis factor alpha, FNIP – fibrous non-specific interstitial pneumonia, AE2 — alveolar epithelium type II cells, ECM – extracellular matrix, EMT — epithelial-mesenchymal transition, FGFR — fibroblast growth factor, GWAS — genome-wide association study, HAT — histone acetyltransferase, HDAC — histone deacetylase, HDACi — histone deacetylase inhibitors, HDM — histone demethylase, HLA — major histocompatibility complex, HMT — histone methyltransferase, IL — interleukin, NGS — next generation sequencing, PDGFR — platelet growth factor, siRNA — small interfering RNA, SNP – single nucleotide polymorphism, SP — surfactant protein, SP-A — surfactant protein A, SP-D — surfactant protein D, TGF-β — tumour growth factor beta, TLR — Toll-like receptor, VEGFR – vascular endothelial growth factor

Introduction

Currently, the term "interstitial lung disease" (ILD) combines a heterogeneous group of pulmonary diseases associated with non-infectious infiltrates, mostly in pulmonary interstitial tissue and alveoli, which sometimes manifest as altered pulmonary pattern and irreversible fibrosis. To date, over 200 clinical entities of ILD are known, which account for over 15 % of all pulmonary

pathologies [2]. Morphologically, interstitial pulmonary fibrosis is associated with progressive replacement of pulmonary tissue with fibrous scar tissue due to excessive release of collagen by mesenchymal cells, myofibroblasts. Over time, this process alters the architecture and function of the organ, which, together with the associated autoimmune inflammation in the lung interstitial tissue, promotes development of marked respiratory distress, which gradually progresses along with the spread of the inflammatory process and aggravation of fibrous changes in the lungs [2], causing a number of unfavourable clinical and prognostic effects [8]. The course and outcome of the disease significantly depend on the specific clinical entity of ILD; therefore, early disease verification and forecasting the course of the disease are crucial (Fig. 1).

There is currently a group of ILDs with known causes, which includes HSP associated with exposure to various organic (mould spores, particulate bird droppings, non-tuberculous mycobacteria, etc.) and non-organic substances (silicone dioxide, asbestos, coal mine dust, beryllium and solid metals), as well as a number of medicinal products. Also, this group includes ILDs caused by systemic autoimmune rheumatic disorders [8, 42]. A new classification of chronic HSP proposes to separate non-fibrous and fibrous variants. In terms of clinical, functional and visual properties, the latter can be non-progressive or progressive [3]. There are reports of ILDs with progressive drug-induced fibrosis, for instance, caused by amiodarone [8], and also in patients with rheumatoid arthritis and systemic scleroderma [41]. Among ILDs with unknown origin, or idiopathic interstitial pneumonias (IIP), there is a subgroup of diseases with chronic fibrous X-ray morphologic pattern, which includes usual interstitial pneumonia (UIP) and fibrous non-specific interstitial pneumonia (FNIP). An excellent example of an ILD with X-ray morphologic pattern of UIP is IPF, which is progressive in 100 % of cases. For reference, FNIP is progressive only in 65 % of cases. The majority of IIPs are sporadic; however, according to the contemporary view, genetic susceptibility can have a significant role not only in manifestation, but also in the variant of ILD course [3, 8, 42].

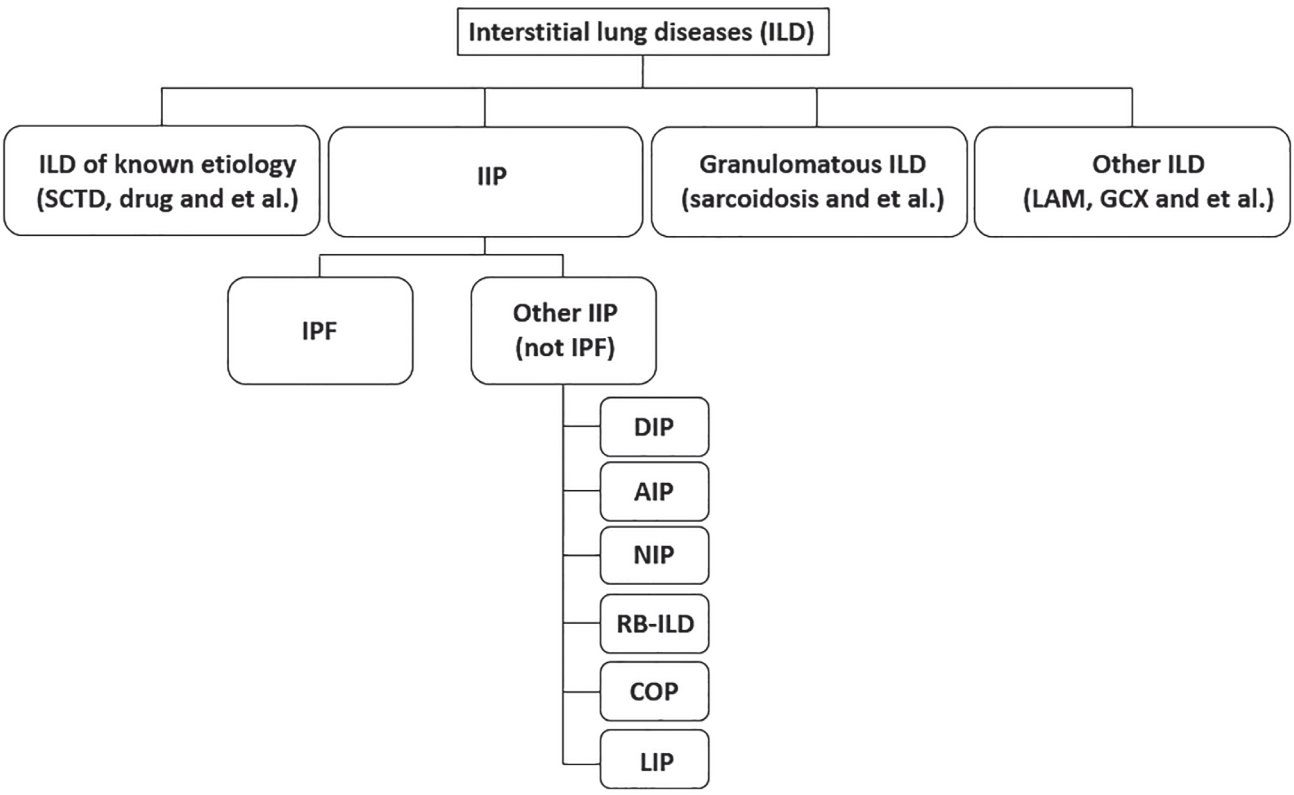

Figure 1. *Classification of ILD*

Note. ILD — interstitial lung diseases, IPF — idiopathic pulmonary fibrosis, IIP — idiopathic interstitial pneumonia DIP — desquamative interstitial pneumonia, RB-ILD — respiratory bronchitis associated with interstitial lung disease, AIP- acute interstitial pneumonia, COP — cryptogenic organizing pneumonia, NIP — non-specific interstitial pneumonia, LIP — lymphoid interstitial pneumonia, SCTD — systemic connective tissue diseases, LAM — lymphangioleiomyomatosis, GCX — histiocytosis X

Given the commonly progressive nature and unfavourable prognosis, ILD rightfully draws the attention of scientists and clinicians all over the world. The incidence of ILD varies between 0.63 and 7.6 per 100,000 people in the USA and Europe [45, 47], with a significant rise in the numbers with population ageing. A recent study of the global disease burden demonstrated that the ILD share in the increase in all-cause deaths in 2017 was 0.26 %, while the number of ILD-associated loss of years of life rose by 86 % over the past two decades [14]. According to the WHO, pre-COVID-19 social losses from ILD were comparable with losses from lung cancer [10].

Given the high rates of disablement and deaths in individuals of employable age resulting from ILD progression and development of irreversible pulmonary fibrosis, where health protection is of utmost importance because of existing demographical fluctuations in the Russian Federation, recently the need in deep studies of the clinical and pathogenetic features of ILD, as well as improvements of the existing and development of efficient approaches to manage this category of patients have become of immediate interest [4, 44]. Nevertheless, despite a number of achievements in the understanding of the pathogenetic mechanisms of the disease, the origin of diseases in this group is understudied, irrespective of the obvious understanding of its complexity and a combination of effects from genetic and epigenetic factors.

Modern idea of the pathogenesis of ILDs

Scientists and clinicians have been actively discussing the role of genetic susceptibility [53], environmental factors [58] and changes related to fast ageing [22] in the development of IPF and HSP, the combination of which results in a complex epigenetic re-programming, promoting aberrant activation of epithelial cells. When activated, epithelial cells release a lot of mediators, which promote migration, proliferation and activation of fibroblasts and myofibroblasts. These cells are resistant to apoptotic mechanisms and continue releasing extracellular matrix components [36]. Extracellular matrix holds a number of growth factors involved in the upregulation mechanisms and acting as components of cross signal pathways, which also adds to steady remodelling of lung tissue and fibrosis progression [36].

A pathologic result is replacement of the normal elastic extracellular matrix of the lungs with modified matrix rich in fibrillar collagen [61].

Overall, heterogeneous genetic variants can promote development of altered bronchopulmonary tissue, which becomes more susceptible to recurring microdamages under the influence of various potential environmental factors.

This objective of this review is to analyse the results of the modern genetic and epigenetic studies in patients with IPF and HSP, which makes it possible to identify the potential targets for interventions in the course and outcomes in patients with ILDs, most commonly dealt with by a pulmonologist, such as IPF and HSP.

Genetic factors of IPF and HSP development

To date, patients with IPF underwent three genome-wide association studies (GWAS), which identified single nucleotide polymorphisms (SNP) in several loci, associated with predisposition to IPF [19, 38]. These variants included mutations in gene *MUC5B* [35, 48, 54]; in genes related to the innate immunity functioning (*TOLLIP, TLR3, IL1RN, IL8, TGFB1*) [22, 40] and barrier function of epithelial tissue (*DSP, DPP9*) [4, 22], as well as in genes maintaining telomere integrity (*TERT, TERC, OBFC1, TINF2, DKC1, RTEL1, PARN*) [6, 13, 29, 31, 57], surfactant production (*SFTPC, SFTPA2, ABCA3*) [23, 38] and cell cycle regulation (*KIF15, MAD1L1, CDKN1A*) [7, 42] (Fig. 2).

For example, SNP rs35705950 in the promoter region of mucin gene 5B (*MUC5B*) was first identified back in 2011 during a genome-wide association study and is associated with a 7-fold increase in the risk of IPF [37]. After 2011, this SNP in gene MUC5B was verified in numerous independent studies and is still the most significant risk factor associated with development of IPF [23, 43, 48, 54]. Also, several authors reported a paradoxical advantage in the survival rates of patients with IPF, who are heterozygous carriers of a minor allele of this gene, as compared to patients who do not have it [7, 19]. However, other groups of patients with ILD demonstrated that the same mutation variant results in poorer survival rates in patients with interstitial pneumonia with autoimmune manifestations and a trend to poorer survival rates in patients with ILD associated with a connective tissue disorder or chronic HSP [5, 35].

In 2013, the same GWAS identified SNP of two other genes associated with cell-cell adhesion — *DSP* (desmoplakin) and *DPP9* (dipeptidyl peptidase 9), associated with IPF [19]. It has been demonstrated that mutations, which cause loss of function in other desmosome genes, including *DSG1*, boost production of proinflammatory cytokines and promote phagocyte attraction [22, 37].

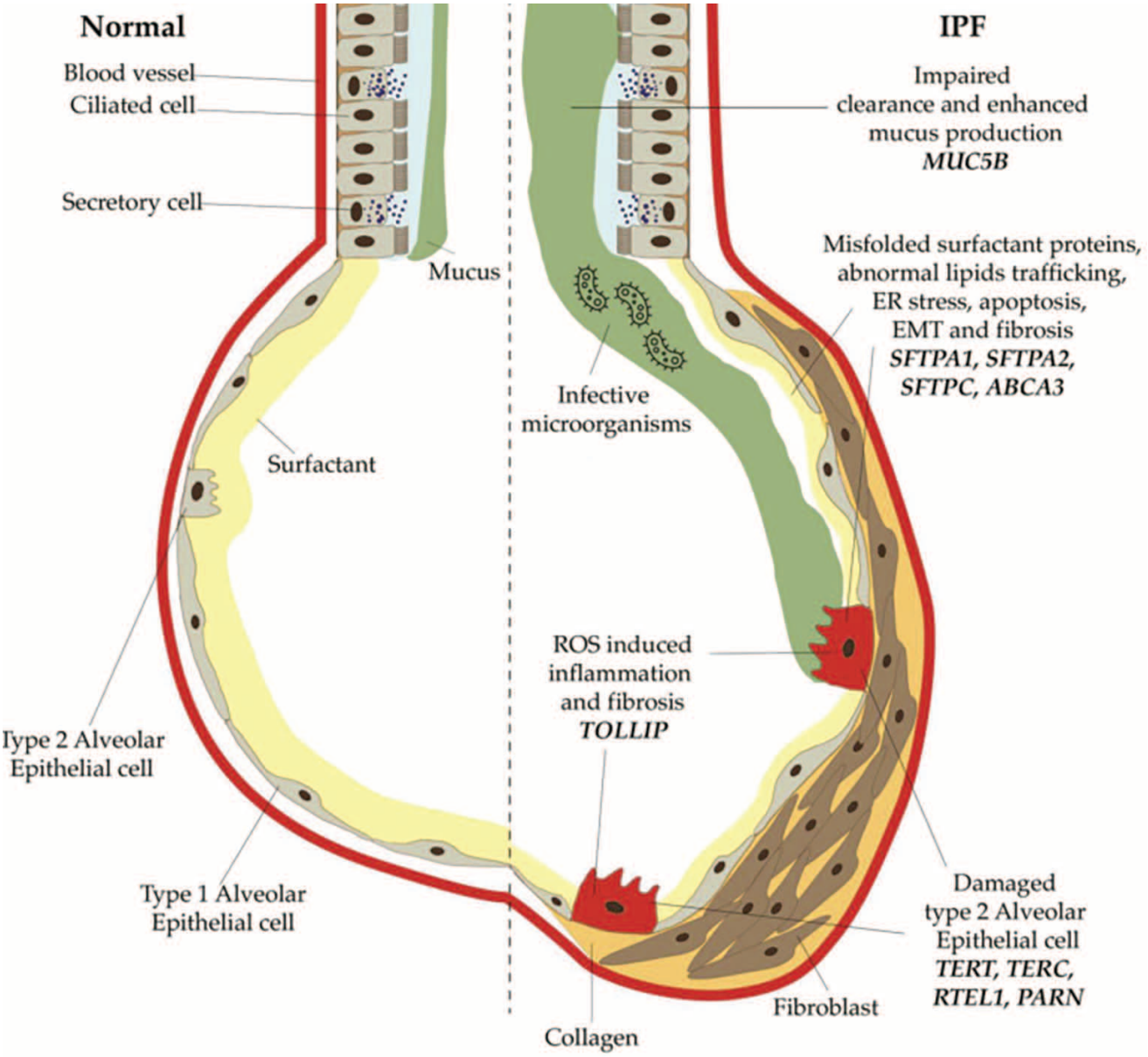

Figure 2.
Key profibrotic mechanisms secondary to mutations or polymorphisms in the genes of telomerase, surfactant proteins, mucin 5B.

Note. Mutations in *TERT, TERC, PARN* and *RTEL1* reduce telomerase activity, which leads to increased telomere shortening. *SFTPC, SFTPA1, SFTPA2, ABCA3* are involved in the modulation and stabilization of alveolar surfactant tension; when altered, they can cause increased endoplasmic reticulum stress, which ultimately leads to epithelial-mesenchymal transitions and apoptosis of type II alveolocytes. Polymorphisms in the *MUC5B* gene are responsible for mucociliary dysfunction with impaired clearance and increased mucus production, predisposing to bacterial overgrowth and infection [63, modified]).

Cytokines, produced both by damaged epithelial cells and activated alveolar cells, including such cytokines as IL-1β, IL-6 and IL-8, facilitate this cyclic damage process [38]. As a result, the epithelial layer of alveoli loses its barrier function, both due to genetic predisposition and stronger inflammatory signals.

Some authors also demonstrated that IPF is associated with impaired regulation of signalling of auto-inflammatory Toll-like receptors as a link between innate and adaptive immune response [23, 38]. Ten functional TLRs have been identified, which have distinct receptor/ligand associations, at the same time they are localised either on the cell membrane (TLR1, 2, 4, 5, 6) or in endosomal compartments (TLR3, 7, 8, 9) in order to recognise various extracellular and endocellular signals, respectively [42]. Genetic risk variants, which impact signalling of TLR family related to IPF, are presented below (Fig. 3).

In 2013, GWAS identified three more common SNPs (rs111521887, rs5743894, rs574389) of the protein gene interacting with Toll-like receptors (*TOLLIP*), which were associated with a high risk of IPF, and one of them (rs5743894) was also associated with high mortality rates

in patients with this disease [19]. TOLLIP is known to be expressed mostly by alveolar macrophages and epithelial cells. Each of the identified SNPs was associated with 20–50 % reduction in *TOLLIP* mRNA expression [19]. Since *TOLLIP* and *MUC5B* are related genes in chromosome 11p15.5 region, there are conflicting data whether their variants are in linkage disequilibrium or ensure independent associations to bring about the risk of IPF [18, 35, 43, 48]. Nevertheless, their expression in epithelial cells is higher in IPF, which is probably a result of long-term exposure to pathogens [16, 24, 25, 39, 40, 43, 52].

An integral part of the normal human lung function and prevention of alveolar collapse during respiration is surfactant protein (SP). It is a well-known fact that surfactant protein is a phospholipid-rich substrate, which is produced by distal parts of the airways, alveolocytes. Approximately 10 % of surfactant consists of proteins produced and released by alveolar epithelium type II cells (AE2) and terminal secretory cells of the airways [8, 42]. Fractions of surfactant protein A (SP-A) and D (SP-D) belong to a specific group of innate immune proteins called collectin, named after calcium-binding C-terminal lectin domain, which recognises respective receptors on pathogen surface [23, 38]. It has been demonstrated that SP-A and SP-D opsonize common bacterial and viral pathogens and promote phagocyte destruction by innate immune cells, such as macrophages and neutrophils. Sparse SNP in two adjacent genes encoding SP-A, *SFTPA1* and *SFTPA2* were described in several cases of family pulmonary fibrosis [4, 33]. However, the role of these and other surfactant-associated SNP in the development of sporadic IPF is still unclear. Several authors reported that patients with IPF had lower SP-A concentration in bronchoalveolar lavage compared to healthy volunteers, and SP-A levels are inversely correlate with patient survival rates [7, 38].

Unlike IPF, patients with HSP did not undergo any large-scale GWAS; however, some studies with target genotyping showed a number of genes responsible for

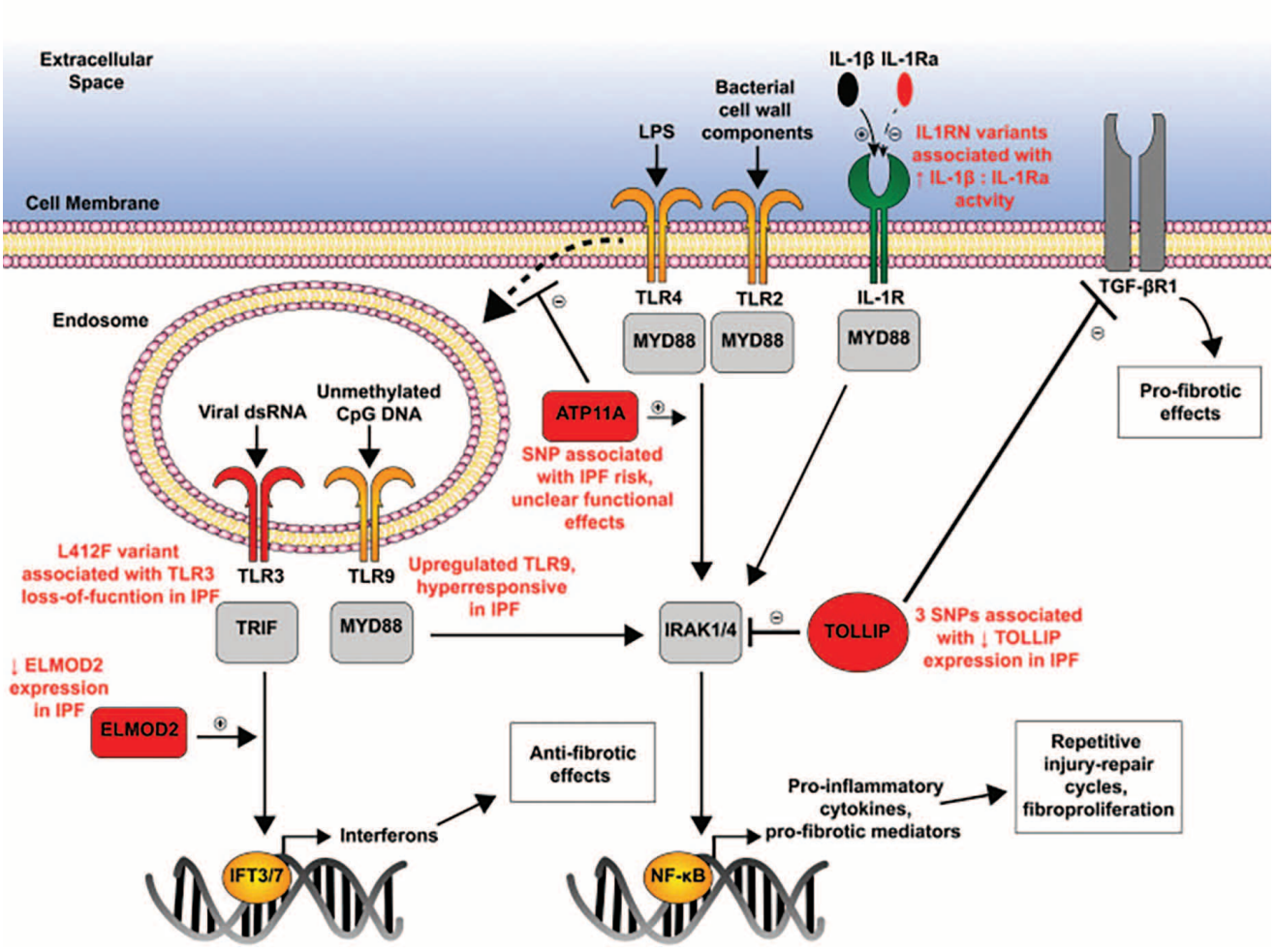

Figure 3. *Pro-fibrous transmission of TLR signals [36, changed]*

higher susceptibility to this disease with an unfavourable outcome. For instance, a test was performed in order to identify SNP in genes of the major histocompatibility complex (HLA) [18]. Gene HLA-DRB1 in patients with HSP had several SNP associated with carrier status of specific antigens and production of tumour necrosis factor alpha (TNF-α) [18].

B. Ley et al. demonstrated that SNP of promoter MUC5B associated with predisposition to IPF is found in a significantly larger number of patients with HSP, as compared to healthy controls [35]. However, unlike patients with IPF, the latter was associated with a higher risk of death in patients with HSP, and the degree of this association varies in various cohorts.

GWAS identified gene polymorphisms which can impact the susceptibility to IPF. A transcriptome analysis of RNA separated from the lung tissue and peripheral blood showed expression of genes involved in the pathogenesis and outcomes of IPF and HSP. These studies demonstrated that, while patients with IPF had higher regulation of genes involved in tissue remodelling, apoptosis and fibroblast signalling, patients with HSP had higher regulation of genes, which are important for the immune function, including genes transmitting T-cell signals and other which are associated with the major histocompatibility complex functioning [38].

Further transcriptome studies of lung and peripheral blood samples of patients with IPF confirmed the role of genes involved in the alveolar epithelium damage and remodelling, i.e. pathogenesis of IPF [23].

As for additional criteria to differentiate IPF and ILDs for the development of a tool to genomically forecast survival rates in patients based on peripheral blood data, transcriptome analysis was used. By using a two-stage multicenter approach to identification and validation, J.D. Herazo-Maya et al. identified a gene signature consisting of 52 differentially expressed genes, which is able to efficiently classify patients with a high or low risk of death during the 4-year follow-up period. This gene signature had test efficiency characteristics similar to those of the validated model of clinical forecasting [23] and significantly improved the existing clinical model. Then these researchers verified the 52-gene signature at six sites across the USA and Europe. It was demonstrated that antifibrotic therapy initiation was associated with favourable gene signature modulation. The majority of differentially expressed genes, which were identified using this approach, are essential for immunological enhancement. It is assumed that impaired immune response regulation can greatly contribute to IPF progression [50].

Studies of large families with several affected family members allowed identifying a number of genes associated with monogenetic forms of family idiopathic pulmonary fibrosis (FPF) and improved our understanding of the genetic basis of this ILD. Currently, there are seven known genes associated with telomeres, which were involved in the development of FPF in adults (*TERT, TERC, RTEL1, PARN, NAF1, TINF2, DKC1*) [15, 33, 42, 59]. Pathogenic variants of genes related to telomeres are associated with extremely short age-adjusted length and predispose to multisystem organ dysfunction, including PF, hepatic dysfunction and bone marrow failure [50].

Pathogenic variants related to telomeres were found in approximately 30 % of all family members with FPF, and *TERT* is the most frequently affected gene, which accounts for up to 20 % of FPF cases [40, 50]. Inheritance of a pathogenic variant related to telomeres results in a considerable risk of ILD; however, other factors, such as age, sex, environmental conditions and telomere length, also contribute to penetration variability [35, 58, 59]. At the same time, correlation between genotype and ILD phenotype in patients with pathogenic telomere-associated variants is weak. Despite the fact that IRF is the most common clinical diagnosis in relatives with FPF, it accounts for less than a half of all cases. The other part includes ILD both with known (HSP and ILD associated with connective tissue disorders) and unknown origin (idiopathic non-specific interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis). Interesting to note that the presence of a rare telomere-associated variant in *TERT, TERC, PARN* or *RTEL1* was associated with rapid disease progression and low survival rates irrespective of the diagnosis [59]. This observation allows assuming that the presence of a pathogenic variant in the telomere-associated gene prevails over the clinical manifestation of the disease, including ILD variant and overall prognosis. The accumulated data show that telomere dysfunction not only predisposes to disease manifestation, but it can also impact the rate of disease progression and the intrazonal nature of fibrosis [15, 59].

Epigenetic effects in IPF and HSP

No doubt that genetic predisposition alone is not sufficient for PF development, and the group of ILDs cannot be characterised without assessment of epigenetic effects. Gene expression is controlled by a number of epigenetic mechanisms, which coordinate activation and suppression of gene transcription (Fig. 4). Epigenetics impacts gene expression modulation irrespective of

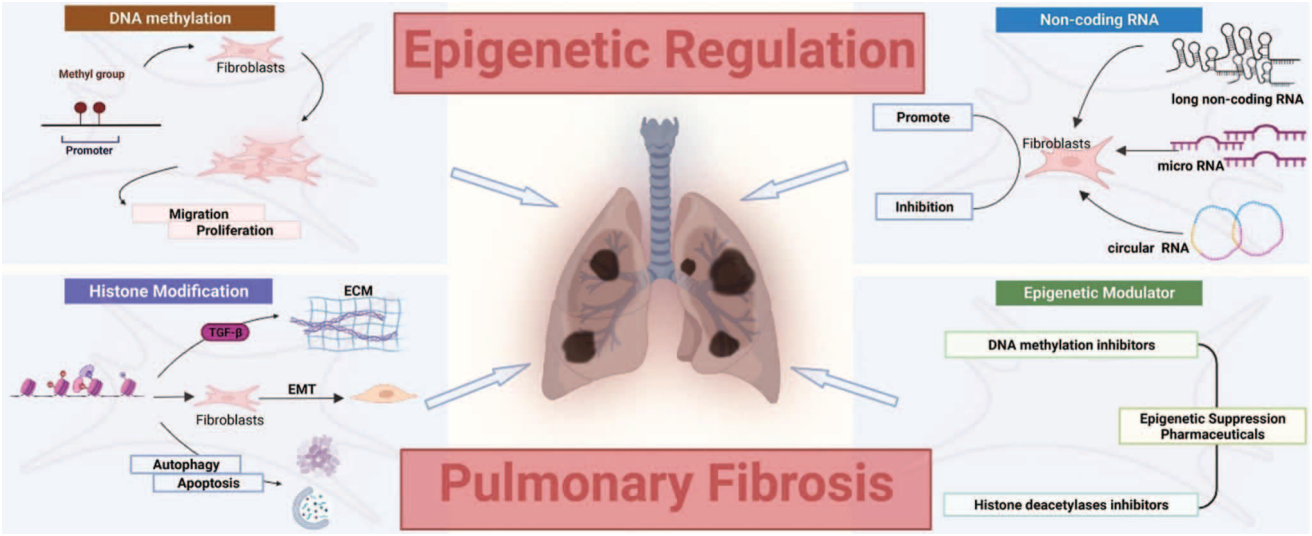

Figure 4. *Key mechanisms of epigenetic changes in the development and course of pulmonary fibrosis [modified, 67]*
Note. ECM — extracellular matrix, EMT — epithelial-mesenchymal transition, TGF-β — transforming growth factor beta)

DNA sequence. Currently, epigenetic modifications can be grouped into three types: DNA methylation in CpG sites, posttranslational modifications of histones and non-coding RNA. A number of studies demonstrated that several genes are differentially expressed in the lungs of ILD patients; this concerns mostly endocellular signal pathways of tumour growth factor beta (TGF-β), epithelial-mesenchymal transition, fibroblast proliferation [28, 55, 62].

The use of *TGF-β*, the main factor promoting ILD development, increases DNMT1 and DNMT3a levels in pulmonary fibroblasts without changing their mRNA expression, using various posttranscriptional mechanisms [31]. Upon interaction with TGF-β1, DNMT3a production increases due to increased protein synthesis and translation. To the contrary, TGF-β1 inactivates glycogen synthase kinase-3β, which causes inhibition of DNMT1 ubiquitination and its proteosomal degradation in pulmonary fibroblasts. The data from the study demonstrate the significant role of DNA methylation in the pathogenesis of ILDs. The most common histone modifications include methylation and acetylation. Histone methylation is regulated by dynamical interaction between two sets of enzymes: histone methyltransferases (HMT) and histone demethylases (HDM). Signature of histone acetylation in a cell plays a role in chromatin structure modulation and gene expression. This dynamic process is regulated by a balance between histone acetyltransferase (HATs) and histone deacetylase (HDAC) activity. Among HATs, the most well-studied protein is p300, which is associated with transcriptional activation of numerous genes in response to cell signalling. It has been demonstrated that increased p300 activity and expression are associated with various diseases, including PF [49] and acute respiratory distress syndrome [12]. Also, it has been shown that genetic deficit and pharmacological inhibition of p300 eliminate pulmonary fibrosis both in vitro and *in vivo* [9]. The role of non-coding RNAs in the pathogenesis of ILD is well-recognised. MicroRNAs are associated with almost all stages of ILD pathogenesis. For instance, let-7d, miR-200, miR-26a and miR-375 are associated with lung epithelium reparation, epithelial to mesenchymal transition (EMT); miR-21, miR-155, miR-26a, miR-27a-3p, miR-9-5p are associated with fibroblast activation and their transdifferentiation to myofibroblasts; and miR-320a is associated with AECII cell ageing and collagen production regulation. Currently available data confirm the dual pathogenetic role of microRNA and involvement both in fibrotic and antifibrotic processes in ILD [9]. Numerous environmental factors, such as behavioural patterns, patient's diet, and drugs taken (widely defined as exposome), ageing factors, which are currently evaluated on the molecular level, can cause epigenetic modifications, thus impacting gene expression.

All biological characteristics of pulmonary fibrosis can be explained by impaired gene expression regulation associated with epigenetic modifications. Given that epigenetic modifications are dynamic, they are an attractive therapy target, because epigenetic markers can be reversed using specific therapies, e.g., histone deacetylase inhibitors (HDACi) [11].

Moreover, individual episignatures actually become disease-specific, and epigenetic profile can be used to

verify clinical diagnosis. Identification of altered methylation, caused by disease progression, is particularly important for pathologies closely related to environmental exposure, like in IPF. Epidemiological studies demonstrated the relationship between exposure to inhaled environmental agents and IPF development, which is true for cigarette smoke, chip dust, metallic dust, silica particles, textile dust, and possibly pollutants found in agricultural, farming and cattle-breeding areas [17, 60, 63]. Cigarette smoke is the highest risk factor of disease development, allowing to assume that it has a significant epigenetic effect, especially in cases of genetic predisposition to the disease [57, 63]. Studies of genome methylation in IPF are ongoing; they aim at identification of specific modified methylation models, which can shed light on the role of environmental impact and pathogenetic mechanisms underlying PF development. Epigenetic signatures can be potential biomarkers for clinical diagnosis verification, identification of new drug therapies in order to reverse epigenetic changes and monitoring effects of available therapies.

Modern approaches to ILD therapy, taking into account possible effects of genetic factors

A recent study, which was based on the next generation sequencing (NGS) results and bioinformatic approaches, described some genetic and epigenetic pathways, which can be affected by an antifibrotic agent nintedanib [56].

Nintedanib is a tyrosine kinase inhibitor, which possesses antifibrotic properties due to the impact and interference with fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and potential inhibition of TGF-β signalling for ECM suppression [61]. It is worth noting that, following nintedanib therapy, authors identified four genes with reduced expression and one gene with increased expression, which impact the following microRNA/mRNA interactions: *E2F1*, *NPTX1*, *DDX11*, *PLXNA4* (reduced expression) and *SLC25A23* (increased expression).

The presence of relatively rare variants of telomere-associated single nucleotide polymorphisms or short telomeres promote faster disease progression both in IPF and HSP patients; however, currently there are no sufficient data on the efficacy of specific therapies.

Another remarkable recent study evaluated the efficacy and safety of nintedanib and pirfenidone in a cohort of PF patients with telomerase gene mutations. The authors found that both antifibrotic therapies were associated with less reduced forced vital capacity without any unexpected side effects [27]. However, the current strategy of immunosuppressive agent use varies depending on the type of lung involvement; for instance, immunosuppressive agents are often prescribed to patients with progressive HSP, while it is not indicated in patients with IPF [30]. The safety and efficacy of immunosupression in patients with short telomerases were not tested systematically. Small samples of patients with rare *TERT* and *TERC* variants allowed assuming that immunosuppressure therapy after lung transplantation due to ILD can be associated with a high rate of side effects, including bone marrow failure, hepatic toxicity and infections [15]. It brings about the question of safety and tolerability of this therapeutic strategy for patients with short telomeres in a wide range of ILDs. Antifibrotic agents, including pirfenidone and nintedanib, are effective in slowing down pulmonary function impairment in patients with IPF [30]. Pirfenidone was well tolerated by a small group of *TERT* carriers, but larger studies are required to identify its efficacy in patients with IPF with telomere dysfunction. One study demonstrated that pirfenidone can slow down the rate of EMT progression by modulating several gene-induced profibrotic pathways [34]. Pirfenidone can suppress enzymes involved in EMT, such as SULF2, and boost the activity of antifibrotic genes, such as Gremlin 2 (GREM2), which then cause restoration of the damaged alveolar epithelium via fibroblast growth factor-10, thus preventing fibrosis. Moreover, the levels of EDN1 and 5-HTR2B, two profibrotic genes, which are associated with collagen deposits and fibroblast proliferation, drop under the effect of pirfenidone.

Since the available medicinal products cannot cure IPF, several studies sought to use gene therapy as a potential strategy in attenuation of a wide array of processes involved in fibrosis. Despite the possible advantages of gene therapy, no studies for the treatment of IPF have been conducted to date. Development of new medicinal products for treatment of IPF is really challenging because of the complex pathogenesis of the disease and sophisticated disease modelling in animals. The currently available animal models are not specific to IPF, they just reproduce some aspects of PF, artificially caused by various chemicals (e.g., bleomycin, FTIC and lipopolyssacharide). Early studies to evaluate the potential use of gene therapy in IPF patients were focused on induction of the targeted gene overexpression using both nanoparticles and viral vectors [46, 64]. This approach

was mainly aimed at inflammatory pathways, including TGF-β and FGF7 signalling pathways [5, 41].

Most recently, the use of gene suppression with siRNA (small interfering RNA) for the management of PF was studied in several studies, which described the efficacy of some siRNA combined with antifibrotic compounds in the therapy of several aspects of PF [20]. Very few studies evaluated the use of miRNA to induce gene expression suppression in PF patients [64, 65]. These studies showed that miRNA-based therapy can have huge potential for simultaneous suppression of several genes associated with fibrosis. However, the pleiotropic effects of miRNA for various gene transcripts (not all of them have been characterised yet) raise concerns about the safety of therapeutic use of these ncRNAs.

In general, these studies confirm the applicability of gene therapy in suppression of fibrosis progression. However, to date, not a single gene therapy approach has demonstrated the ability to reverse confirmed fibrosis.

Future study outlooks

The possibilities of a more thorough study of the genetic and epigenetic principles of PF are the current clinical and scientific task, the addressing of which can help both in diagnostics and gene therapy development for the management of pulmonary diseases associated with fibrosis.

It is obvious that the genetic data can significantly complement the existing algorithms of ILD diagnosis, acting as a molecular foundation for morphological, clinical and instrumental data. According to the diagnostic manoeuvre roadmap proposed by experts at the European Respiratory Society (ERS) and Pulmonary Fibrosis Foundation [26], the current indications for genetic testing are: unexplained ILD in childhood; presence of ILD, first-degree and second-degree family members with ILD; any patient with a relative, who is a carrier of a pathogenic/possible pathogenic ILD variant; any patient with suspected telomere shortness (short telomere syndrome includes pulmonary fibrosis, haemotological disorders and hepatic diseases); any patient with short telomeres, where telomere length is analysed prior to the test; any patient with idiopathic fibrotic interstitial lung disease below 50 years of age.

In addition to the proposed genetic diagnostic roadmap, the European Respiratory Society also considers a possibility of diagnostic testing to identify predisposition to ILD in patients with Hermansky-Pudlak syndrome, because, provided considerable amount of genome data is interpreted correctly, they will be used for diagnostic evaluation of risks of the disease and prevention of its rapid progression and patient incapacitation [32]. At the moment, there are genetic diagnostic testing approaches, which are panels including a specific genome set, e.g., a test panel Interstitial Lung Disease manufactured by Blueprint genetics (USA), comprising the following genes: *ABCA3 (16p13.3), CSF2RA (Xp22.33), CSF2RB (22q12.3), DKC1 (Xq28), ELMOD2 (4q31.1), HPS1 (10q24.2), HPS4 (22q12.1), ITGA3 (17q21.33), NF1 (17q11.2), NKX2-1 (14q13.3), PARN (16p13.12), RTEL1 (20q13.33), SFTPA1 (10q22.3), SFTPA2 (10q22.3), SFTPB (2p11.2), SFTPC (8p21.3), SLC34A2 (4p15.2), SLC7A7 (14q11.2), SMPD1 (11p15.4), STAT3 (17q21.2), TERC (3q26.2), TERT (5p15.33), TINF2 (14q12), TSC1 (9q34.13), TSC2 (16p13.3)* [1]. New data on genetic variants of predisposition to ILD have been accumulated, which help to improve and make new genetic diagnostic panels.

Interference with epigenetic changes contributing to the development and progression of PF is also an interesting scientific and research perspective for target precision therapy in this category of patients [9].

Conclusion

The significance of genetic and epigenetic studies is becoming more and more important for the study of pathogenesis, identification of disease progression and prognosis in patients with ILD. A lot of genes and pathways involved in PF development have been found as a result of genome-wide studies. A major part of currently available genome data is associated with patients with IPF. As far as patients with HSP and other forms of ILD are concerned, very few similar studies have been conducted. To date, there is no unified standardisation of diagnostic criteria for ILD variants. Also, it is still unclear how to classify these groups of patients depending on the risk of disease progression and death, including identification of genetic factors, namely predictors of unfavourable disease outcome in patients with HSP. More and more articles study the effects of epigenetic modifications, which can alter the risk of the disease in the presence of environmental triggers. Besides, epigenetic mechanisms can impact development and prognosis of PF. DNA methylation in CpG sites, posttranslational histone modifications and suppression of non-coding RNA genes are the mechanisms, actively studied in fibrogenesis to search for potential clinical use as biomarkers and targets for drug therapy, because epigenetic markers can be reversed.

Finally, there are data on molecular pathways both on genetic and epigenetic levels, which are the foundation for the efficient antifibrotic therapy.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Юренев Г.Л.: редактирование текста

Author contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Lyamina S.V.: formulation of the idea, development of the research methodology, collection, analysis and systematization of data, preparation and design of the manuscript

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Список литературы / References:

1. Данные генетического регистра. [Электронный ресурс]. URL: https://www.ncbi.nlm.nih.gov/gtr/tests/552741/. (дата обращения 11.09.2024).
   Data from the genetic registry. [Electronic resource]. URL: https://www.ncbi.nlm.nih.gov/gtr/tests/552741/. (date of the application 11.09.2024) [In Russian]
2. Интерстициальные болезни легких: практическое руководство под ред. Н.А. Мухина. М.: Литера. 2007; 432 с.
   Interstitial lung diseases: a practical guide edited by N.A. Mukhin. M.: Litera. 2007; 432 p. [In Russian]
3. Визель А.А., Горблянский Ю.Ю., Илькович М.М. и др. Фиброзирующий саркоидоз: от понимания к перспективе лечения. Практическая пульмонология. 2021; 1: 61-73.
   Viesel A.A., Gorblyansky Yu.Yu., Ilkovich M.M., et al. Fibrotic sarcoidosis: from understanding to treatment perspective. Practical pulmonology. 2021; 1: 61-73. [in Russian]
4. Бирюкова С.С., Вишневский А.Г., Гимпельсон В.Е. и др. Как увеличить человеческий капитал и его вклад в экономическое и социальное развитие. Тезисы докладов к XIX Апрельской международной научной конференции по проблемам развития экономики и общества, под ред. Кузьминова Я.И., Овчаровой Л.Н., Якобсона Л.И. Москва, Изд. дом Высшей школы экономики. 2018; 38-46.
   Biryukova S.S., Vishnevsky A.G., Gimpelson V.E., et al. How to increase human capital and its contribution to economic and social development. Abstracts of reports for the XIX April International Scientific Conference on Problems of Economic and Social Development, ed. Kuzminova Ya.I., Ovcharova L.N., Yakobson L.I. Moscow, Publishing House of the Higher School of Economics. 2018; 38-46. [In Russian]
5. Adegunsoye A., Oldham J.M., Fernandez Perez E.R., et al. Outcomes of immunosuppressive therapy in chronic hypersensitivity pneumonitis. ERJ Open Res. 2017; 3: 00016–2017. doi: 10.1183/23120541.00016-2017.
6. Alder J.K., Stanley S.E., Wagner C.L., et al. Exome sequencing identifies mutant TINF2 in a family with pulmonary fibrosis. Chest. 2015; 147: 1361–8. doi: 10.1378/chest.14-1947.
7. Allen R.J., Porte J., Braybrooke R., et al. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. Lancet Respir Med. 2017; 5: 869–80. doi: 10.1016/S2213-2600(17)30387-9.
8. Antoine M.H., Mlika M. Interstitial Lung Disease.In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2024. [Electronic resource]. URL: https://www.ncbi.nlm.nih.gov/books/NBK541084/ (date of the application: 02.05.2024).
9. Avci E., Sarvari P., Savai R., et al. Epigenetic Mechanisms in Parenchymal Lung Diseases: Bystanders or Therapeutic Targets? Int J Mol Sci. 2022; 23(1): 546. doi: 10.3390/ijms23010546.
10. Raghu G., Remy-Jardin M., Myers J.L., et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018; 198(5): e44–e68. doi: 10.1164/rccm.201807-1255ST.
11. Bartczak K., Białas A.J.; Kotecki M.J., et al. More than a Genetic Code: Epigenetics of Lung Fibrosis. Mol. Diagn. Ther. 2020; 24: 665–681. doi: 10.1007/s40291-020-00490-7.
12. Chen Y., Huang Z., Bao Y., et al. Increased p300/CBP expression in acute respiratory distress syndrome is associated with interleukin-17 and prognosis. Clin. Respir. J. 2020; 14: 791–799. doi: 10.1111/crj.13197.
13. Cogan J.D., Kropski J.A., Zhao M., et al. Rare variants in RTEL1 are associated with familial interstitial pneumonia. Am J Respir Crit Care Med. 2015; 191: 646–55. doi: 10.1164/rccm.201408-1510OC.
14. Collaborators GBDCRD. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020; 8: 585–96. doi: 10.1016/S2213-2600(20)30105-3].
15. Dai J., Cai H., Li H., et al. Association between telomere length and survival in patients with idiopathic pulmonary fibrosis. Respirology. 2015; 20: 947–52. doi: 10.1111/resp.12566.
16. Dickson R.P., Erb-Downward J.R., Martinez F.J., et al. The microbiome and the respiratory tract. Annu Rev Physiol. 2016; 78: 481–504. doi: 10.1146/annurev-physiol-021115-105238.
17. Ding Q., Luckhardt T., Hecker L., et al. New Insights into the Pathogenesis and Treatment of Idiopathic Pulmonary Fibrosis. Drugs. 2011; 71: 981–1001. doi: 10.2165/11591490-000000000-00000.

18. Falfán-Valencia R., Camarena A., Pineda C.L., et al. Genetic susceptibility to multicase hypersensitivity pneumonitis is associated with the TNF-238 GG genotype of the promoter region and HLA-DRB1*04 bearing HLA haplotypes. Respir Med. 2014; 108: 211–217. doi: 10.1016/j.rmed.2013.11.004.
19. Fingerlin T.E., Murphy E., Zhang W., et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet, 2013; 45: 613–20. doi: 10.1038/ng.2609.
20. Garbuzenko O.B., Ivanova V., Kholodovych V., et al. Combinatorial treatment of idiopathic pulmonary fibrosis using nanoparticles with prostaglandin E and siRNA(s). Nanomed. Nanotechnol. Biol. Med. 2017; 13: 1983–1992. doi: 10.1016/j.nano.2017.04.005
21. Hannum G., Guinney J., Zhao L., et al. Genome-wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates. Mol. Cell. 2013; 49: 359–367. doi: 10.1016/j.molcel.2012.10.016.
22. Hao Y., Bates S., Mou H., et al. Genome-Wide Association Study: Functional Variant rs2076295 Regulates Desmoplakin Expression in Airway Epithelial Cells. Am J Respir Crit Care Med. 2020; 202(9): 1225-1236. doi: 10.1164/rccm.201910-1958OC.
23. Herazo-Maya J.D., Sun J., Molyneaux P.L., et al. Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. Lancet Respir Med. 2017; 5: 857–68. doi: 10.1016/S2213-2600(17)30349-1.
24. Hewitt R.J., Molyneaux P.L. The respiratory microbiome in idiopathic pulmonary fibrosis. Ann Transl Med. 2017; 5: 250. doi: 10.21037/atm.2017.01.56.
25. Huang Y., Ma S.F., Espindola M.S., et al. Microbes are associated with host innate immune response in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2017; 196: 208–19. doi: 10.1164/rccm.201607-1525OC.
26. Killian H., Ozaki M., Philippot Q., et al. A roadmap to precision treatments for familial pulmonary fibrosis. eBioMedicine. EBioMedicine. 2024; 104: 105135. doi: 10.1016/j.ebiom.2024.105135.
27. Justet A., Klay D., Porcher R., et al. Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation. Eur. Respir. J. 2021; 57: 2003198. doi: 10.1183/13993003.03198-2020.
28. Kaminski N. Microarray analysis of idiopathic pulmonary fibrosis. Am. J. Respir. Cell Mol. Biol. 2003; 29(3): S32–S36.
29. Kannengiesser C., Borie R., Ménard C., et al. Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis. Eur Respir J. 2015; 46: 474–85. doi: 10.1183/09031936.00040115
30. King Jr T.E., Bradford W.Z., Castro-Bernardini S., et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370: 2083–92. doi: 10.1056/NEJMoa1402582.
31. Koh H.B., Scruggs A.M., Huang S.K. Transforming growth factor-β1 increases DNA methyltransferase 1 and 3a expression through distinct post-transcriptional mechanisms in lung fibroblasts. J. Biol. Chem. 2016; 291: 19287–19298.
32. Krishna R. Genetic Testing in Interstitial Lung Disease: Potential Benefits and Unintended Risks. Curr Pulmonol Rep. 2023; 12: 228–238.
33. Kropski J.A., Mitchell D.B., Markin C., et al. A novel dyskerin (DKC1) mutation is associated with familial interstitial pneumonia. Chest. 2014; 146: e1–7. doi: 10.1378/chest.13-2224.
34. Kwapiszewska G., Gungl A., Wilhelm J., et al. Transcriptome profiling reveals the complexity of pirfenidone effects in idiopathic pulmonary fibrosis. Eur. Respir. J. 2018; 52: 1800564. doi: 10.1183/13993003.00564-2018.
35. Ley B., Newton C.A., Arnould I., et al. The MUC5B promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study. Lancet Respir Med. 2017; 5: 639–47. doi: 10.1016/S2213-2600(17)30216-3.
36. Martinez F.J., Collard H.R., Pardo A., et al. Idiopathic pulmonary fibrosis. Nat. Rev. Dis. Prim. 2017; 3: 17074. doi: 10.1038/nrdp.2017.74.
37. Mathai S.K., Pedersen B.S., Smith K., et al. Desmoplakin Variants Are Associated with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016; 193(10): 1151-60. doi: 10.1164/rccm.201509-1863OC.
38. Michalski J.E., Schwartz D.A. Genetic Risk Factors for Idiopathic Pulmonary Fibrosis: Insights into Immunopathogenesis. J Inflamm Res. 2021; 13: 1305-1318. doi: 10.2147/JIR.S280958.
39. Molyneaux P.L., Maher T.M. Respiratory microbiome in IPF: cause, effect, or biomarker? Lancet Respir Med. 2014; 2: 511-513. doi: 10.1016/S2213-2600(14)70088-8.
40. Molyneaux P.L., Willis-Owen S.A.G, Cox M.J., et al. Host-microbial interactions in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2017; 195: 1640–50. doi: 10.1164/rccm.201607-1408OC.
41. Nakao A., Fujii M., Matsumura R., et al. Transient gene transfer and expression of Smad7 prevents bleomycin-induced lung fibrosis in mice. J. Clin. Investig. 1999; 104: 5–11. doi: 10.1172/JCI6094.
42. Newton C.A., Molyneaux P.L., Oldham J.M. Clinical Genetics in Interstitial Lung Disease.Front. Med. 2018; 5: 116. doi: 10.3389/fmed.2018.00116.
43. Oldham J.M., Ma S.F., Martinez F.J., et al. TOLLIP, MUC5B, and the response to N-acetylcysteine among individuals with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015; 192: 1475–82. doi: 10.1164/rccm.201505-1010OC.
44. Olson A.L., Gifford A.H., Inase N., et al. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. Eur. Respir. Rev. 2018; 27(150): 180077. doi: 10.1183/16000617.0077-2018.
45. Olson A.L., Brown K.K., Swigris J.J. Understanding and optimizing health-related quality of life and physical functional capacity in idiopathic pulmonary fibrosis. Patient Relat Outcome Meas. 2016; 7: 29–35. doi: 10.2147/PROM.S74857.
46. Povedano J.M., Martinez P., Serrano R., et al. Therapeutic effects of telomerase in mice with pulmonary fibrosis induced by damage to the lungs and short telomeres. eLife. 2018; 7: e31299. doi: 10.7554/eLife.31299.
47. Raghu G., Chen S.-Y., Hou Q., et al. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. Eur Respir J. 2016; 48: 179–86. doi: 10.1183/13993003.01653-2015.

48. Roy M.G., Livraghi-Butrico A., Fletcher A.A., et al. Muc5b is required for airway defence. Nature. 2014; 505: 412–6. doi: 10.1038/nature12807.
49. Rubio K., Singh I., Dobersch S., Sarvari P., Günther S., Cordero J., Mehta A., Wujak L., Cabrera-Fuentes H., Chao C.-M., et al. Inactivation of nuclear histone deacetylases by EP300 disrupts the MiCEE complex in idiopathic pulmonary fibrosis. Nat. Commun. 2019; 10: 1–16. doi: 10.1038/s41467-019-10066-7.
50. Ryerson C.J., Vittinghoff E., Ley B., et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest.2014; 145: 723–8. doi: 10.1378/chest.13-1474.
51. Sakamoto S., Yazawa T., Baba Y., et al. Keratinocyte Growth Factor Gene Transduction Ameliorates Pulmonary Fibrosis Induced by Bleomycin in Mice. Am. J. Respir. Cell Mol. Biol. 2011; 45: 489–497. doi: 10.1165/rcmb.2010-0092OC.
52. Salisbury M.L., Han M.K., Dickson R.P., Molyneaux PL. Microbiome in interstitial lung disease: from pathogenesis to treatment target. Curr Opin Pulm Med. 2017; 23: 404–10. doi: 10.1097/MCP.0000000000000399.
53. Schwartz D.A. Idiopathic Pulmonary Fibrosis Is a Genetic Disease Involving Mucus and the Peripheral Airways. Ann. Am. Thorac. Soc. 2018; 15(S3): S192–S197. doi: 10.1513/AnnalsATS.201802-144AW.
54. Seibold M.A., Wise A.L., Speer M.C., et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011; 364: 1503–12. doi: 10.1056/NEJMoa1013660.
55. Selman M., Pardo A., Barrera L., et al. Gene Expression Profiles Distinguish Idiopathic Pulmonary Fibrosis from Hypersensitivity Pneumonitis. Am. J. Respir. Crit. Care Med. 2006; 173: 188–198. doi: 10.1164/rccm.200504-644OC.
56. Sheu C.-C., Chang W.-A., Tsai M.-J., et al. Gene Expression Changes Associated with Nintedanib Treatment in Idiopathic Pulmonary Fibrosis Fibroblasts: A Next-Generation Sequencing and Bioinformatics Study. J. Clin. Med. 2019; 8: 308. doi: 10.3390/jcm8030308.
57. Steele M.P., Speer M.C., Loyd J.E., et al. The Clinical and Pathologic Features of Familial Interstitial Pneumonia (FIP) Am. J. Respir. Crit. Care Med. 2005; 172: 1146–1152. doi: 10.1164/rccm.200408-1104OC.
58. 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: 512–7. doi: 10.1038/ng.3278.
59. Stuart B.D., Lee J.S., Kozlitina J., et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. Lancet Respir Med. 2014; 2: 557–65. doi: 10.1016/S2213-2600(14)70124-9.
60. Taskar V.S., Coultas D.B. Is idiopathic pulmonary fibrosis an environmental disease? Proc. Am. Thorac. Soc. 2006; 3: 293–298. doi: 10.1513/pats.200512-131TK.
61. Thannickal V.J., Henke C.A., Horowitz J.C., et al. Matrix biology of idiopathic pulmonary fibrosis: A workshop report of the national heart, lung, and blood institute. Am. J. Pathol. 2014; 184: 1643–1651. doi: 10.1016/j.ajpath.2014.02.003.
62. Tirelli C., Morandi V., Valentini A., et al. Multidisciplinary Approach in the Early Detection of Undiagnosed Connective Tissue Diseases in Patients With Interstitial Lung Disease: A Retrospective Cohort Study. Front. Med. 2020; 7: 11. doi: 10.3389/fmed.2020.00011.
63. Tirelli C., Pesenti C., Miozzo M., et al. The Genetic and Epigenetic Footprint in Idiopathic Pulmonary Fibrosis and Familial Pulmonary Fibrosis: A State-of-the-Art Review. Diagnostics. 2022; 12: 3107.
64. Watanabe M., Ebina M., Orson F.M., et al. Hepatocyte Growth Factor Gene Transfer to Alveolar Septa for Effective Suppression of Lung Fibrosis. Mol. Ther. 2005; 12: 58–67. doi: 10.1016/j.ymthe.2005.02.019.
65. Yuan J., Li P., Pan H., et al. miR-542-5p Attenuates Fibroblast Activation by Targeting Integrin α6 in Silica-Induced Pulmonary Fibrosis. Int. J. Mol. Sci. 2018; 19: 3717. doi: 10.3390/ijms19123717.
66. Zhang S., Liu H., Liu Y., et al. miR-30a as Potential Therapeutics by Targeting TET1 through Regulation of Drp-1 Promoter Hydroxymethylation in Idiopathic Pulmonary Fibrosis. Int. J. Mol. Sci. 2017; 18: 633. doi: 10.3390/ijms18030633.
67. Zhang Y.S., Tu B., Song K. et al. Epigenetic hallmarks in pulmonary fibrosis: New advances and perspectives. Cell Signal. 2023; 110: 110842.doi: 10.1016/j.cellsig.2023.110842.

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