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ROLE OF MICRORNA AND POLYMORPHISMS OF FOXP3 AND ADRB2 GENES IN PATHOGENESIS OF PULMONARY DISEASES

Abstract. The study of the key mechanisms of the development of bronchopulmonary diseases as asthma and chronic obstructive pulmonary disease (COPD) and asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS) are the current directions of molecular medicine. Genetic predisposition as well as influence of environmental factors play an important role in the development of asthma and COPD which are multifactorial diseases. Epigenetic mechanisms also affect regulation of gene expression during asthma, COPD and ACOS. The epigenetic regulation includes methylation of DNA, microRNA, histone modifications and they are all induced by influence of environmental factors. Higher levels of methylation of FOXP3 and ADRB2 DNA are at a higher risk of asthma development. However, there is not enough evidence on the level of methylation of the FOXP3 and ADRB2 genes and microRNA in patients with COPD and ACOS. It should be noted that the epigenetic labels established during the study of cancer and autoimmune disorders have shown their value as biomarkers of diagnosis. In this case, the study of genetic and epigenetic mechanisms of asthma, COPD and ACOS is a relevant objective of biomedicine because it helps to explain the interaction between genes and environmental factors in order to develop diagnosis and personalized treatment for the patients with bronchopulmonary diseases.

Keywords: microRNA, FOXP3 gene, ADRB2 gene, asthma, COPD, ACOS.

Asthma and chronic obstructive pulmonary disease (COPD) are the most frequent chronic lung diseases worldwide. It is estimated that 300 million individuals suffer from asthma worldwide, with increased prevalence in both adults and children [1]. COPD affects an estimates 10% of the world's population, and is the fourth leading cause of death worldwide [2]. Both asthma and COPD are characterized by chronic airway inflammation and airflow obstruction [3,4]. In recent years, a separate condition has been identified - the Asthma and COPD Overlap Syndrome (ACOS) [5]. COPD and asthma have clear differences, but some patients may present with a symptoms of both diseases. Differential diagnosis of ACOS from asthma and COPD is increasingly important, since ACOS has a poor prognosis and different treatment guidelines [6].

Asthma and COPD are related to multifactorial diseases, in the development of which an important role is played by both genetic predisposition and the influence of environmental factors. A variety of genes associated with asthma and COPD have been found [7]. There are genes specific to each disease, as well as genes involved in both diseases [8]. It has been shown that genetic polymorphism gives only a low or moderate level of predisposition to pulmonary diseases, which does not allow explaining the increase in the prevalence of IgE-mediated allergic syndromes. In addition, the mechanism of interaction between genetic and environmental factors in asthma, COPD and ACOS is not clear. In this regard, often genetic and epigenetic analyzes are carried out together. In the study of epigenetic effects, the potential impact of genetic variability is often taken into account [9,10]. Epigenetic regulation includes DNA methylation,

histone modifications and non-coding RNAs (microRNAs), all of which are induced by environmental factors, nutrition, diseases and processes associated with aging [11]. In recent years, there is increasing evidence that epigenetic mechanisms affect the regulation of gene expression in chronic lung diseases such as asthma and COPD. Violation of DNA methylation, modification of histone, specific expression of microRNA and other changes in chromatin organization contribute to reprogramming the immune response of T-cells in early childhood, disrupting the functioning of dendritic cells and activating macrophages. Similar regulation of asthma and COPD occurs in the adult state [12].

There is increasing evidence that regulatory T-cells (Treg-cells) plays an important role in suppressing allergic sensitization and production of immunoglobulin E in the upper respiratory tract in response to the allergen effect. One of the factors that play an important role in the development and functioning of Treg cells is the transcription factor FOXP3 (*Forkhead box transcription factor 3*). Methylation of the transcriptional regulatory regions of the FOXP3 gene suppresses the expression of Foxp3 and, ultimately, the function of Treg-cells [13]. Thus, it is likely that, under the influence of environmental factors, there is an increase in methylation at the FOXP3 locus and this can lead to a decrease in the level of expression of FOXP3 and a decrease in the functioning of Treg-cells.

It has been shown that an increase in DNA methylation levels in the 5'-region of the FOXP3 gene is associated with the level of air pollution by particulate exhaust emissions from diesel engines. In addition, it has been demonstrated that children with higher levels of methylation of FOXP3 DNA are at a higher risk of developing asthma [14]. In carrying out oral specific immunotherapy with food and pollen allergens, it was shown that children resistant to treatment had a low level of methylation of FOXP3, while in children who lost sensitivity to significant allergens, methylation of FOXP3 increased [15]. Similarly, the status of methylation of FOXP3 varies depending on the concentration of immunoglobulin E in serum [16]. However, data on the level of methylation of the FOXP3 gene in patients with COPD and ACOS are absent and its role in the pathogenesis of the above diseases needs more detailed study.

The FOXP3 gene is located on the X chromosome (Xp11.23), has a size of 1296 bp and contains 11 coding and 3 non-coding exons. The FOXP3 gene belongs to a family of molecular complexes that includes histone deacetylases and acetyltransferases, as well as other transcription factors [13]. Figure 1 shows a diagram of the structure of the FOXP3 gene.

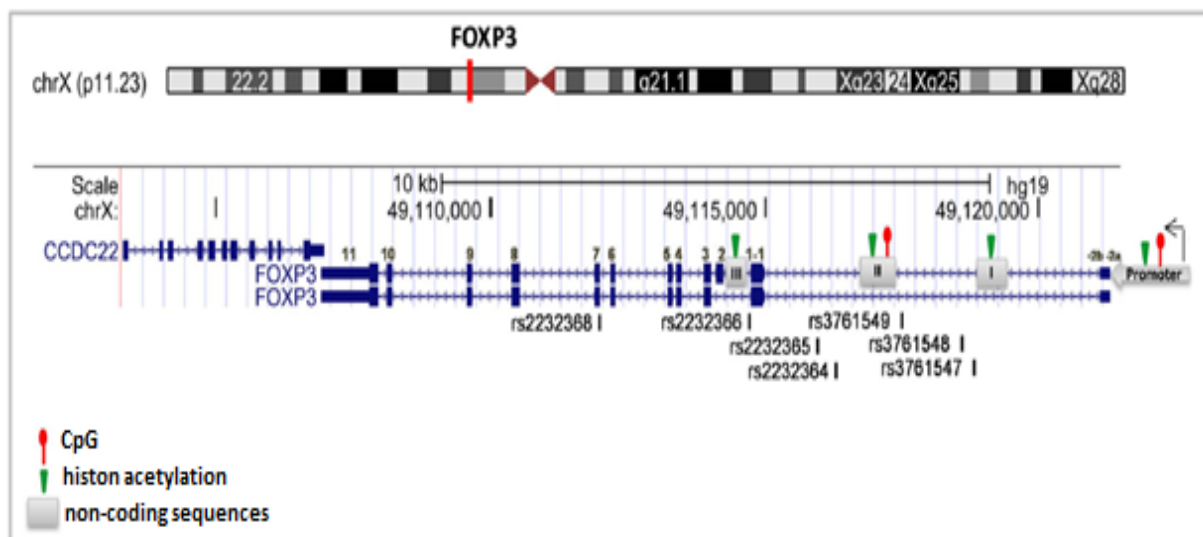


Figure 1 - Schematic view of the FOXP3 gene. The figure shows two isoforms of the gene [13]

The FOXP3 gene has more than one hundred single nucleotide polymorphisms (SNP), many of which are associated with various diseases, including cancer [17]. However, there is very little information about the association of SNP in the FOXP3 gene and allergic atopy, including asthma. Table 1 provides information on all known SNPs in the FOXP3 gene associated with allergic atopy.

Table 1 - SNPs in the FOXP3 gene associated with allergic atopy

SNP	Alleles	Type of disease	Literary source
rs2232368	A / G	Allergic rhinitis	[18] Zhang et al., 2009.
rs6609857	C / T	Bronchial asthma	[19,20] Bottema et al., 2010 a, b
rs3761548	A / C	Allergic rhinitis, bronchial asthma	[18-21] Fodor et al., 2011; Bottema et al., 2010 a, b; Zhang et al., 2009.
rs2232365	A / G	Allergic rhinitis	[22] Hassannia et al., 2011.
rs56066773	C / T	Allergic and autoimmune diseases	[23] Pacheco-Gonzalez et al., 2016.
<i>Continuation of table 1</i>			
rs2232368	A / G	Allergic rhinitis	[18] Zhang et al., 2009.
rs6609857	C / T	Bronchial asthma	[19,20] Bottema et al., 2010 a, b;
rs3761548	A / C	Allergic rhinitis, bronchial asthma	[18-21] Fodor et al., 2011. Bottema et al., 2010 a, b; Zhang et al., 2009.
rs2232365	A / G	Allergic rhinitis	[22] Hassannia et al., 2011.
rs56066773	C / T	Allergic and autoimmune diseases	[23] Pacheco-Gonzalez et al., 2016.

Chu and colleagues [24] showed that from the four SNPs in the FOXP3 gene: rs2280883, rs3761548, rs3761549 and rs5902434, only the last of these SNPs (rs5902434) is associated as with the FOXP3 mRNA level and as well with the reduced risk of COPD.

Another gene with an established effect on asthma is the Adrenoceptor beta 2 (ADRB2) gene. The ADRB2 gene has clinically significant associated polymorphisms with various phenotypes of asthma. So polymorphism *Arg16Gly* is associated with increased repression of gene transcription and a decrease in the number of receptors on the cell surface. The *Gln27Glu* variant is associated with a severe course of asthma [25]. It is known that single nucleotide polymorphisms have a pronounced ethnic and population specificity. It has been shown that the 5'-untranslated region of the ADRB2 gene has a large number of CpG sequences [26]. In addition, several researchers have found that a high level of methylation of this region of the ADRB2 gene is associated with the development of severe asthma in children [27]. From this point of view will be very interesting to study the contribution of methylation of the ADRB2 gene to the pathogenesis of COPD and ACOS. Another aspect of close attention in the treatment of asthma are Multi-Drug Resistance Genes (MDR), which plays a critical role in the development of drug resistance in both prokaryotes and eukaryotes [28]. MDR-1 gene products, such as MRP1 (Multidrug Resistance Protein 1), P-glycoprotein (P-gp) and LRP (Low Density lipoprotein receptor-related protein1), have been shown to act as antioxidants and protect lung tissue from oxidative stress. MDR-1 gene polymorphism can be a major genetic risk factor for developing asthma through increasing in oxidative stress [29]. Studies conducted on the Chinese population showed a correlation between the genetic polymorphisms MDR1-C3435T and G2677T/A with the status of methylation of the MDR1 promoter region [30]. Another level of epigenetic regulation of genome activity in response to effect of environmental factors, in addition to methylation, is a change in the expression of microRNAs.

MicroRNAs (microRNA) are becoming increasingly important in research as new regulators of gene expression, which play a central role in various pathophysiological processes. It has been shown that these classes of non-coding regulatory RNA are involved in several aspects of inflammation, which is the defining sign of many lung diseases such as asthma, COPD, ACOS and lung cancer [31,32]. In addition, in the context of reactive reactions, microRNAs play a central role in the regulation of expression of key proteins that control the type and the immune response of the body. MicroRNAs are important modifiers of the immune system and regulate human defense mechanisms. The function of microRNAs in lung development and the role of these molecules in many pulmonary pathologies have been studied [33]. In lung tissue, there is a unique and conservative profile of microRNA expression [31].

MicroRNAs in the lungs can be organized into three groups depending on the biological functions performed. The first group is microRNA, which is important for lung development, homeostasis and

physiological functions. Here, the level of microRNA expression varies at different stages of lung development, from the embryonic stage to the postnatal period. To this group belongs such microRNAs as miR-200c, miR-195, miR-26a, let-7, miR-29, miR15/miR-16, miR-223 [34]. miR-200c and miR-195 are highly specific for lung tissue. miR-26a targets the transcription factor SMAD-1, which is involved in the process of lung development. The cluster miR17-29 is most pronounced in early embryogenesis of the lungs and decreases significantly throughout the development. Significant expression of miR17-92 is found in lung cancer [35]. The second group of microRNAs is represented by molecules that participate in inflammatory processes occurring in the lung. This group includes miR-146a and miR-146b, which play a central role in the activity of *IL-1 β* at the onset of inflammation. Overexpression of these microRNAs results in a decrease in the regulation of *TNF- α* and other pro-inflammatory cytokines [36]. The third group of microRNA is directly involved in lung functions associated with the pathophysiology of pulmonary diseases. One of the first studies in this field showed that approximately 50% of mice with miR-155 deficiency had spontaneously developed asthma-like states, characterized by an increase of Th2-type cytokines and a large number of lymphocytes and macrophages, but with a similar number of eosinophils as compared to wild-type mice [37]. In other studies it was found that the expression of several miRNAs, including miR-155, is dysregulated in the airways and/or in lymphocytes of patients with asthma [38]. miR-126 expression has been shown to increase in the respiratory tract of mice exposed to house dust mite allergens, and inhibition of miR-126 by using intranasal administration of the miR-126 antagonist decreases the allergic response and blood eosinophil levels in model animals [39]. Some studies have shown that miR-21 expression increased in the mouse model of asthma and it was associated with the Th2 response and the level of *IL-12* expression [40]. Moreover, the absence of miR-21 in CD4 + T cells resulted in reduction in *IL-4* levels and an increase in γ -interferon levels [41]. Examination of the profile of microRNA expression in the blood of patients diagnosed with asthma and COPD, unlike the animal model, is not numerous [42,43]. Wang and colleagues identified a change in the expression level of miR-145-5p, miR-636, miR-338-3p, miR-4485, miR-1229-3p, miR-4707-3p and miR-3620-3p in the serum of patients with asthma, compared with patients with COPD [44]. Roff and colleagues [45] demonstrated a decrease in the level of miR-570-3p in the serum of the patients with asthma.

Our bioinformatic search for microRNAs, the target of which are the key genes involved in the pathogenesis of pulmonary diseases (asthma, COPD, ACOS) by using TargetScan 7.1 programs (www.TargetScan.org), microRna (www.microrna.org), miRanda and miRTarAsthmase, showed that FOXP3 can be targeted for hsa-miR-34a-5p, hsa-miR-34c-5p, hsa-miR-449b-5p and hsa-miR-125a-3p, ADRB2 mRNA has a binding site in the 3'UTR region with hsa-miR-34b-3p, MDR-1 may be the target for the hsa-miR-4262 microRNA, hsa-miR-181d-5p, hsa-miR-181a-5p, hsa-miR-181b-5p, hsa-miR-181c-5p. In the literature there is no data on the association of the above-mentioned microRNAs with asthma, COPD, and ACOS (<http://mirandola.iit.cnr.it/adsearch.php>).

Previous observations have shown that microRNAs can be in a free state in the form of oligonucleotides in plasma and serum, sputum, and other body fluids such as saliva and cerebrospinal fluid. Moreover, free circulating microRNAs in the blood plasma are quite stable, which makes them promising for the development of a biomarker system for the diagnosis of lung diseases [32]. We have already developed a system of markers for the lung cancer diagnosis, by estimating the level of three free plasma circulating microRNAs: hsa-miR-19b-3p, hsa-miR-125b and hsa-miR-155-5p [46, 47]. There is few data in the literature about the microRNAs expression level in the plasma of patients with asthma and COPD. There are no studies about the role of free circulating microRNAs in pathogenesis of ACOS [48]. It seems very relevant to analyze the role of microRNAs in the pathogenesis of major obstructive diseases such as asthma and COPD and to develop the biomarker system for ACOS based on the analysis of the free plasma circulating microRNAs.

To date, more attention is paid to personalized medicine, which implies the appointment of a specific drugs to patients on the base of pharmacokinetic and pharmacogenomic informations. Existing asthma management and treatment methods are aimed at controlling symptoms and mainly include fast-acting *beta*₂-adrenoceptor agonists and corticosteroids for long-term monitoring, but these therapies are non-effective in the control of severe asthma. Therefore, one of the important issues of asthma research is how microRNAs affect the development of corticosteroid resistance in the asthma treatment. There are the results that the microRNAs expression level in the human bronchial epithelial cell line (BEAS-2B) is

changed in response to treatment with an antileukotriene drug - Montelukast (MNT), which widely used for the treatment of asthma [49]. Another study showed that miR-146a expression decreased in CD8+ and CD4+ T-cells in atopic dermatitis patients with oral corticosteroid treatment [50]. It was shown that expression of miR-126 and miR-21 in epithelial cells of the respiratory tract in patients taking inhaled corticosteroids was significantly reduced [51]. Thus, it can be concluded that microRNAs can be used not only for diagnostic purposes, but also serve as molecular biomarkers for testing pulmonary diseases. The study of genetic and epigenetic mechanisms assist to understand the interaction between genes and environmental factors to develop new diagnosis and personalized treatment of the patients.

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МИКРОРНК ЖӘНЕ FOXP3, ADRB2 ГЕНДЕРІ ПОЛИМОРФИЗМІНІҢ ӨКПЕ АУРУЛАРЫНДАҒЫ РӨЛІ

Аннотация. Демікпе, өкпенің созылмалы обструктивті аурулары (ӨСОА) және өкпенің созылмалы обструктивті ауруы және бронх демікпесі айқас синдромы (ӨБДАС) секілді бронх-өкпе ауруларының даму механизмдерін зерттеу молекулалық медицинаның өзекті бағыты болып табылады. ӨСОА дамуларында генетикалық бейімділік пен қоршаған орта факторларының әсері маңызды рөл атқаратын мультифакториалды аурулар қатарына жатады. Эпигенетикалық механизмдер демікпе, ӨСОА, ӨБДАС кезінде гендер экспрессиясының реттелуіне әсер етеді. Эпигенетикалық реттелуге микроРНК, ДНК метилденуі, гистондардың модификациясы жатады, сонымен қатар олар қоршаған орта факторларының әсерімен индуцирленеді. FOXP3, ADRB2 гендерінің метилдену деңгейінің жоғарылауына байланысты демікпе ауруының даму қаупі басым болып келеді. Алайда, ӨСОА мен ӨБДАС бар науқастарда FOXP3, ADRB2 гендерінің метилдену деңгейі туралы мәліметтер аз. Айта кететін жағдай, қатерлі ісік аурулары мен аутоиммундық ауытқуларды зерттеуде анықталған эпигенетикалық таңбалау диагностика үшін сапалы биомаркер екендігін көрсетті. Осыған байланысты Демікпе, ӨСОА және ӨБДАС эпигенетикалық және генетикалық механизмдерді зерттеу биомедицинаның өзекті міндеті болып табылады, себебі, гендер мен қоршаған орта факторларының арасында өзара байланыстарды түсінуге көмектесе отырып, жаңа диагностикалық және өкпе-бронх ауруларымен ауыратын науқастарға жеке емдеу тәсілдерін қолдануға мүмкіндік береді.

Түйін сөздер: микроРНК, FOXP3 гені, ADRB2 гені, демікпе, ӨСОА, ӨБДАС.

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РОЛЬ МИКРОРНК И ПОЛИМОРФИЗМА FOXP3 И ADRB2 ГЕНОВ В ПАТОГЕНЕЗЕ БРОНХОЛЕГОЧНЫХ ЗАБОЛЕВАНИЙ

Аннотация. Изучение ключевых механизмов развития бронхолегочных заболеваний, таких как астма, хроническая обструктивная болезнь легких (ХОБЛ) и синдром перекрытия бронхиальной астмы и ХОБЛ (СПБАХ) является актуальным направлением молекулярной медицины. Астма и ХОБЛ относятся к мультифакториальным заболеваниям, в развитии которых важную роль играет как генетическая предрасположенность, так и воздействие факторов окружающей среды. Эпигенетические механизмы также влияют на регуляцию экспрессии генов при астме, ХОБЛ и СПБАХ. Эпигенетическое регулирование включает метилирование ДНК, микроРНК, гистоновые модификации, причем все они индуцированы воздействием факторов окружающей среды. Более высокие уровни метилирования ДНК FOXP3 и ADRB2 подвержены более высокому риску развития астмы. Однако мало известно о роли метилирования генов FOXP3 и ADRB2 и микроРНК у пациентов с ХОБЛ и СПБАХ. Следует отметить, что эпигенетические метки, установленные при изучении раковых заболеваний и аутоиммунных расстройств показали свою ценность в качестве биомаркеров диагностики. В этой связи изучение генетических и эпигенетических механизмов БА, ХОБЛ и СПБАХ является актуальной задачей биомедицины, поскольку помогает объяснить взаимодействие между генами и факторами окружающей среды для разработки диагностики и персонализированного лечения пациентов с бронхолегочными заболеваниями.

Ключевые слова: микроРНК, FOXP3 гены, ADRB2 гены, астма, ХОБЛ, СПБАХ.

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