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NAD-DEPENDENT DEACETYLASE GENES OF SIRTUIN FAMILY AND RISK OF DEVELOPING VARIOUS PHENOTYPES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic respiratory diseases with high morbidity and mortality. The pathogenesis of COPD is closely related to oxidative stress, that is the main mechanism causes accelerated cell senescence. Published data suggest that the COPD pathogenesis may involve stress responses dysregulation that inhibit cellular senescence. We aimed to assess the contribution of sirtuin genes (*SIRT2, SIRT1, SIRT3, SIRT6*) to the various COPD phenotypes risk.

SNPs of *SIRT2* (rs10410544), *SIRT1* (rs3758391, rs3818292), *SIRT3* (rs3782116, rs536715), *SIRT6* (rs107251) genes were genotyped by the real-time polymerase chain reaction (PCR) among 1245 samples (severe COPD with frequent exacerbations (N=331), stable COPD with rare exacerbations (N=290) and control (N=624)). Logistic regression was used to detect the association of studied SNPs in different models.

Significant associations with severe COPD phenotype were identified for *SIRT1* (rs3818292) (P=0.0097, OR = 1.49 for AG genotype), *SIRT3* (rs3782116) (P = 0.0034, OR =0.63) and *SIRT3* (rs536715) (P = 0.00001, OR =0.53) under dominant model, and *SIRT6* (rs107251) (P = 0.00001, OR =0.55 for CT genotype). Stable COPD phenotype with rare exacerbations was associated with *SIRT1* (rs3818292) (P = 0.0055, OR =1.54 for AG genotype), *SIRT3* (rs536715) (P = 0.00001, OR =0.48 under dominant model), and *SIRT6* (rs107251) (P = 0.0002, OR =0.54 for CT genotype).

The obtained results indicate the contribution of NAD-dependent deacetylase genes of sirtuin family and cellular senescence mechanisms to COPD development. The *SIRT3* (rs3782116) identified as a specific marker for severe COPD phenotype with frequent exacerbations.

Keywords: Chronic obstructive pulmonary disease; sirtuins; oxidative stress

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Introduction. Chronic obstructive pulmonary disease (COPD) is a multifactorial chronic heterogeneous inflammatory disease of the respiratory system, with a predominant injury of the distal respiratory tract and lung parenchyma [6]. COPD is characterized by the development of systemic effects that cause the severe complications further aggravating the course of the disease in patients. COPD is one of the most common chronic respiratory diseases with high morbidity and mortality rates [6].

Tobacco smoking is the principal risk factors of COPD; however, COPD develops as result of complex interaction between genetic and environmental factors [4; 6]. Further research is needed to understanding the pathobiology of COPD. At the moment, another aspect of COPD pathogenesis is being discussed, that the COPD pathogenesis may involve stress responses dysregulation that inhibit cellular senescence [4]. Oxidative stress is a key factor in accelerated cellular senescence [8]. Many endogenous molecules counteract to cellular senescence and NAD-dependent protein deacetylases from the sirtuins family are considered as potential factors that decrease senescence [15]. Sirtuin deficiency is considered as one of the mechanisms of accelerated lung aging in COPD [4; 10]. Sirtuins are involved in the formation and functioning of mitochondria, mtDNA protection, and thus may play a key role in the pathogenesis of age-associated diseases [5].

We aimed to assess the contribution of NAD-dependent protein deacetylases from the sirtuins family genes (*SIRT2, SIRT1, SIRT3, SIRT6*) to the various COPD phenotypes risk.

Materials and methods. DNA samples were collected from unrelated subjects who were Tatars in ethnicity and resided in the Republic of Bashkortostan. The study was approved by the Ethics Committee at the Institute of Biochemistry and Genetics (Protocol No 17, December 7, 2010, №19, November 11, 2022). All participants of this study provided written

Table 1

Genotypes and alleles distribution of sirtuins genes loci in studied groups

Gene. SNP	Genotypes and alleles	COPD абс. (%)	Control абс. (%) (N=624)	P
Severe COPD with frequent exacerbations (N=331)				
SIRT2 rs10410544 T>C	CC/CT/TT	144/134/53 (43.50/40.48/16.01)	254/271/99 (40.71/43.43/15.87)	0.653
	C/T	422/240 (63.75/36.25)	779/469 (62.42/37.58)	0.602
SIRT1 rs3758391 T>C	TT/TC/CC	104/131/96 (31.42/39.58/29.00)	168/294/162 (26.92/47.12/25.96)	0.081
	T/C	339/323 (51.21/48.79)	630/618 (50.48/49.52)	0.799
SIRT1 rs3818292 A>G	AA/AG/GG	175/144/12 (52.87/43.50/3.63)	375/213/36 (60.10/34.13/5.77)	0.011
	A/G	494/168 (74.62/25.38)	963/285 (77.16/22.84)	0.236
SIRT3 rs3782116 G>A	GG/GA/AA	165/118/48 (49.85/35.65/14.50)	239/287/98 (38.30/45.99/15.71)	0.002
	G/A	448/214 (67.67/32.33)	765/483 (61.30/38.70)	0.007
SIRT3 rs536715 G>A	GG/GA/AA	222/73/36 (67.07/22.05/10.88)	324/249/51 (51.92/39.90/8.17)	0.00001
	G/A	517/145 (78.10/21.90)	897/351 (71.88/28.13)	0.004
SIRT6 rs107251 C>T	CC/CT/TT	212/86/33 (64.05/25.98/9.97)	333/243/48 (53.37/38.94/7.69)	0.00001
	C/T	510/152 (77.04/22.96)	909/339 (72.84/27.16)	0.052
Stable COPD with rare exacerbations (N=290)				
SIRT2 rs10410544 T>C	CC/CT/TT	128/116/46 (44.14/40.00/15.86)	254/271/99 (40.71/43.43/15.87)	0.575
	C/T	372/208 (64.14/35.86)	779/469 (62.42/37.58)	0.512
SIRT1 rs3758391 T>C	TT/TC/CC	81/133/76 (27.93/45.86/26.21)	168/294/162 (26.92/47.12/25.96)	0.930
	T/C	295/285 (50.86/49.14)	630/618 (50.48/49.52)	0.919
SIRT1 rs3818292 A>G	AA/AG/GG	148/129/13 (51.03/44.48/4.48)	375/213/36 (60.10/34.13/5.77)	0.01
	A/G	425/155 (73.28/26.72)	963/285 (77.16/22.84)	0.08
SIRT3 rs3782116 G>A	GG/GA/AA	129/111/50 (44.48/38.28/17.24)	239/287/98 (38.30/45.99/15.71)	0.097
	G/A	369/211 (63.62/36.38)	765/483 (61.30/38.70)	0.368
SIRT3 rs536715 G>A	GG/GA/AA	201/76/13 (69.31/26.21/4.48)	324/249/51 (51.92/39.90/8.17)	0.00001
	G/A	478/102 (82.41/17.59)	897/351 (71.88/28.13)	0.00001
SIRT6 rs107251 C>T	CC/CT/TT	184/75/31 (63.45/25.86/10.69)	333/243/48 (53.37/38.94/7.69)	0.00001
	C/T	443/137 (76.38/23.62)	909/339 (72.84/27.16)	0.121

Notes: P-value for Chi-square test

informed consent. The COPD group included 621 patients (539 (86.79%) males and 82 (13.21%) females) with a mean age of 64.42±10.71 years. There were 510 (82.13%) smokers and former smokers, the smoking index was 45.34±23.84 pack years; and 111 (17.87%) nonsmokers. In order to identify genetic markers associated with COPD phenotypes, the control group and patients were compared; COPD patients differentiated according to the modern classification which included an integral assessment of the COPD phenotype, taking into account the number of exacerbations per year, the results of specialized questionnaires: the COPD assessment test (CAT - COPD Assessment Test), the Medical Research Council Dyspnea Scale (MRC - Medical Research Council Dyspnea Scale) and indicators of the study of lung function [7]. Two phenotypes were identified: group 1 – severe COPD with frequent exacerbations (**N=331**), with a mean age of 65.39±10.01 years; group 2 - COPD with rare exacerbations (**N=290**), with a mean age of 65.03±8.17 years. The control group included 624 subjects (555 (88.94%) males and 69 (11.06%) females) with a mean age of 59.67±12.31. There were 526 (84.29%) smokers and former smokers and 98 (15.71%) nonsmokers in the group; the smoking index was 38.75±24.87 pack years in the smokers. Inclusion and exclusion criteria for the COPD and control have been previously described [2].

Genotyping. DNA was isolated from peripheral blood leukocytes by phenol–chloroform extraction. The set included SNPs of the following genes: *SIRT1* (rs3758391, rs3818292), *SIRT2* (rs10410544), *SIRT3* (rs3782116, rs536715), *SIRT6* (rs107251). SNP genotyping was performed by real-time polymerase chain reaction (PCR) using commercial kits for fluorescence detection (DNK-Sintez, Russia; https://www.oligos.ru) and a BioRad CFX96™ instrument (Bio-Rad Laboratories, United States). The methods of analysis were described in detail previously [2]. *Statistical Analyses.* Statistical analyses of the results were performed using the software packages IBM SPSS 22.0. The methods were described in detail previously [2].

Results and discussion. Data on the distribution of genotypes and alleles frequencies of the studied loci, and the significance of differences between groups in the frequencies of genotypes and alleles of *SIRT1* (rs3758391, rs3818292), *SIRT2* (rs10410544), *SIRT3* (rs3782116, rs536715), *SIRT6* (rs107251) genes

Table 2

Significant association of studied sirtuins genes loci with COPD stratified by phenotypes

Gene, SNP	Rare allele	N	Genotype / model	OR_{adj} (CI95%)	P_{adj}	$P_{cor-FDR}$
Severe COPD with frequent exacerbations (N=331)						
SIRT1 rs3818292 A>G	G	955	AA AG+GG dominant	1.00 1.35 (1.01-1.81)	0.046	0.046
			AA+GG AG	1.00 1.49 (1.10-2.00)	0.0097	0.0125
SIRT3 rs3782116 G>A	A	955	GG GA+AA dominant	1.00 0.63 (0.46-0.86)	0.0034	0.0068
			AA+GG AG	1.00 0.66 (0.48-0.90)	0.0088	0.0125
			Log-additive	0.77 (0.62-0.97)	0.022	0.0244
SIRT3 rs536715 G>A	A	955	GG GA+AA dominant	1.00 0.53 (0.39-0.72)	0.00001	0.000033
			AA+GG AG	1.00 0.43 (0.30-0.59)	0.00001	0.000033
			Log-additive	0.74 (0.59-0.94)	0.01	0.0125
SIRT6 rs107251 C>T	T	955	CC CT+TT dominant	1.00 0.65 (0.48-0.86)	0.003	0.0068
			CC+TT CT	1.00 0.55 (0.40-0.75)	0.00001	0.000033
Stable COPD with rare exacerbations (N=290)						
SIRT1 rs3818292 A>G	G	914	AA AG+GG доминантная	1.00 1.45 (1.08-1.96)	0.015	0.015
			AA+GG AG	1.00 1.54 (1.14-2.08)	0.0055	0.007
SIRT3 rs536715 G>A	A	914	GG GA+AA доминантная	1.00 0.48 (0.35-0.66)	0.00001	0.000035
			AA+GG AG	1.00 0.53 (0.38-0.75)	0.0002	0.00035
			лог-аддитивная	0.55 (0.42-0.72)	0.00001	0.000035
SIRT6 rs107251 C>T	T	914	CC CT+TT доминантная	1.00 0.66 (0.48-0.89)	0.0061	0.0071
			CC+TT CT	1.00 0.54 (0.39-0.75)	0.0002	0.00035

Note: N - is the number of individuals included in the analysis; Padj, significance in the likelihood ratio test for the regression model adjusted for age, sex, smoking status and pack-years; ORadj, adjusted odds ratio and CI, 95% confidence interval; Pcor-FDR, significance after the FDR correction; in the log-additive model per rare allele dosage, the rare allele dosage increases in the following order: homozygote for the common allele (0)–heterozygote (1)–homozygote for the rare allele (2).

are presented in Table 1. The groups of patients with severe COPD and healthy controls differed significantly in the genotypes and / or alleles frequency distributions of *SIRT1* (rs3818292), *SIRT3* (rs3782116, rs536715), *SIRT6* (rs107251) genes. Statistically significant results of association analysis of studied gene loci and severe COPD are shown in Table 2.

An association of *SIRT1* (rs3818292) with severe COPD phenotype was established in the dominant model (P_{adj} = 0.046, OR = 1.35); the risk of COPD was increased in heterozygous individuals (P_{adj} = 0.0097, OR = 1.49). The rs3782116 and rs536715 of *SIRT3* gene were also associated with severe COPD; thus for rs3782116, the association was statistically significant in the dominant (P_{adj} = 0.0034, OR =0.63) and additive (P_{adj} = 0.022, OR =0.77) models, and with the heterozygous genotype (P_{adj} = 0.0088, OR = 0.66). The most significant associations were established for the *SIRT3* (rs536715) in the dominant model (P_{adj} = 0.00001, OR = 0.53) and the heterozygous genotype (P_{adj} = 0.00001, OR = 0.48) and the *SIRT6* (rs107251) with the heterozygous CT genotype (P_{adj} = 0.00001, OR=0.55).

Association with stable COPD phenotype was detected to *SIRT1* (rs3818292) in dominant model (P_{adj} = 0.015, OR =1.45) and heterozygous genotype (P_{adj} = 0.0055, OR =1.54); *SIRT3* (rs536715) in dominant (P_{adj} = 0.00001, OR =0.48) and additive (P_{adj} = 0.00001, OR =0.55) models and heterozygous genotype (P_{adj} = 0.0002, OR =0.53). *SIRT6* (rs107251) associated with stable COPD phenotype in the dominant model (P_{adj} = 0.0061, OR =0.66), significant association was established for heterozygous CT genotype of *SIRT6* (rs107251 (P_{adj} = 0.0002, OR =0.54) (Table 2).

SIRT1 is the most studied member of the mammalian sirtuin family. It has been shown that *SIRT1* plays an important role in signaling pathways involved in cellular senescence and cell death [5]. *SIRT1* deacetylates many key regulatory proteins and transcription factors involved in DNA repair, inflammation, expression of antioxidant genes, and cellular senescence [14]. Previously, it was shown that SIRT1 levels are reduced in peripheral pulmonary and peripheral blood mononuclear cells of patients with COPD [12]. We found that the risk of developing both COPD phenotypes is higher in heterozygous carriers of the *SIRT1* (rs3818292).

SIRT3 is the main mitochondrial deacetylase regulating many enzymes involved in energy metabolism, respiratory chain components, the tricarboxylic acid cycle, ketogenesis, and fatty acid beta-oxidation [15]. *SIRT3* can directly control the production of reactive oxygen species (ROS) by deacetylating manganese-superoxide dismutase (SOD2), the main mitochondrial antioxidant enzyme [13]. SIRT3 plays a pro- and anti-apoptotic role in various pathological conditions [15]. We have studied the association of two functional polymorphisms (rs3782116 and rs536715) of the *SIRT3* gene with different COPD phenotypes. The association with the development of severe COPD with frequent exacerbations was established for both polymor-

phic loci, while in stable COPD association was shown only with the rs536715 locus. Our data indicated that *SIRT3* (rs3782116) gene locus is the specific marker of frequent exacerbations COPD phenotype.

The associations of *SIRT3* gene loci with age-associated diseases in which oxidative stress and cellular senescence play a key role were extensively investigated [11].

The *SIRT6* (rs107251) is associated with the development of both COPD phenotypes. *SIRT6* exhibits ADP-ribosyltransferase and histone deacetylase activity, and plays role in DNA repair [9]. In the study [3], a decrease of *SIRT6* levels was shown in respiratory epithelial cells of COPD patients due to cigarette smoke exposure. An association of *SIRT6* gene loci with cardiovascular diseases has been shown; cardiovascular diseases are often a comorbid pathology in COPD and have similar pathogenetic mechanisms associated with oxidative stress and cellular senescence [1].

Conclusion. As a result of the study, we have identified significant associations with the development of various COPD phenotypes with polymorphic variants of the *SIRT1* (rs3818292), *SIRT3* (rs536715) and *SIRT6* (rs107251) genes. A specific marker for COPD phenotype with frequent exacerbations is the *SIRT3* (rs3782116) gene locus. The data obtained confirm the hypothesis of a significant role of NAD-dependent protein deacetylases from the sirtuin family and the mechanisms of cellular senescence in the hereditary predisposition to COPD development.

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MATURATION OF MONOCYTES INTO DENDRITIC CELLS BY MORPHOLOGICAL SIGNS IN BREAST CANCER

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Taking into account the complex maturation process of dendritic cells under culturing conditions, as well as the available data of morphological characteristics at various pathological conditions, we find it interesting to assess the features of cell morphology in oncological patients. The purpose of this study was to assess the morphological characteristics of the processes of maturation of dendritic cells in breast cancer. In cancer patients, the potential for cellular viability and maturation compared to healthy individuals is reduced in the early days of cultivation, probably due to the cytotoxicity of chemotherapy and radiation therapy at the time of the study. Cell analysis in the last days of cultivation indicates that the processes of activation of monocyte maturation in dendritic cells in in vitro were significantly higher in oncobols than in healthy individuals.

Keywords: cultivation, monocytes, dendritic cells, morphology, breast cancer.

Introduction. Anticancer vaccines are designed to induce an immune response against tumor antigens. Despite decades of research and development, only a few anti-cancer vaccines have been approved for human use. The success of