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Т-РЕГУЛЯТОРНЫЕ ЛИМФОЦИТЫ И ЯДЕРНАЯ ТРАНСЛОКАЦИЯ FoxP3 В РАЗЛИЧНЫХ ДЕПО ЖИРОВОЙ ТКАНИ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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Резюме. Регуляторные Т-лимфоциты (Treg) присутствуют в жировой ткани. Их относительное содержание, а также уровень ядерной транслокации FoxP3 в эпикардиальной и тимус-замещающей жировой ткани остаются неизученными. В то же время свойства резидентных Treg в жировой ткани могут иметь большое значение у пациентов с ишемической болезнью сердца как потенциальный патофизиологический фактор развития атеросклероза. Целью исследования являлось сравнение содержания FoxP3$^+$Treg-лимфоцитов и ядерной транслокации FoxP3 в эпикардиальной, тимусной, подкожной жировой ткани и периферической крови у пациентов с ишемической болезнью сердца. Пилотное исследование включало 11 пациентов с ишемической болезнью сердца, у которых в плановом порядке было проведено аортокоронарное шунтирование после предшествующей селективной коронарографии. Частоту CD4$^+$CD25^{hi}FoxP3$^+$ и CD4$^+$CD25^{lo}FoxP3$^+$ лимфоцитов и уровень ядерной транслокации FoxP3 оценивали методом проточной цитометрии с визуализацией в периферической крови и стромально-сосудистой фракции эпикардиальной, подкожной и тимусной жировой ткани. Доля CD4$^+$CD25^{hi}FoxP3$^+$ и CD4$^+$CD25^{lo}FoxP3$^+$ лимфоцитов была выше в эпикардиальной жировой ткани по сравнению с кровью (в 3 и 5 раз, $p = 0,020$); доля CD4$^+$CD25^{lo}FoxP3$^+$ клеток в подкожной жировой ткани была в 4 раза выше, чем в крови ($p = 0,028$). Уровень ядерной транслокации FoxP3 был максимальным в крови и снижался в эпикардиальной, подкожной и тимусной жировой ткани ($p = 0,020$ как для CD4$^+$CD25^{hi}FoxP3$^+$, так и для CD4$^+$CD25^{lo}FoxP3$^+$ лимфоцитов). Доля CD4$^+$CD25^{lo}FoxP3$^+$ клеток была прямо связана с возрастом в тимусной ($r_s = 0,818$; $p = 0,002$) и обратно пропорционально – в

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эпикардиальной жировой ткани (r_s = -0,618; p = 0,043). Доли $CD4^+CD25^{hi}FoxP3^+$ и $CD4^+CD25^{lo}FoxP3^+$ клеток с ядерной транслокацией FoxP3 в подкожной жировой ткани отрицательно коррелировали с возрастом (r_s = -0,827; p = 0,002 и r_s = -0,648; p = 0,031 соответственно). Доля $CD4^+CD25^{lo}FoxP3^+$ клеток с ядерной транслокацией FoxP3 в тимусной жировой ткани отрицательно коррелировала с соотношением окружности талии и бедер (r_s = -0,700; p = 0,016). Тяжесть атеросклероза была связана только с долей $CD4^+CD25^{lo}FoxP3^+$ клеток в подкожной жировой ткани (r_s = -0,655; p = 0,029). Таким образом, эпикардиальная и подкожная жировая ткань обогащены Treg, но факторы, влияющие на накопление Treg и ядерную транслокацию FoxP3 в этих жировых депо, могут различаться. Полученные результаты в дальнейшем могут быть использованы для персонификации иммуномодулирующей терапии у больных атеросклерозом.

Ключевые слова: эпикардиальная жировая ткань, тимус, Т-регуляторные лимфоциты, FoxP3, субклеточная локализация, атеросклероз, ишемическая болезнь сердца

T REGULATORY LYMPHOCYTES AND FoxP3 NUCLEAR TRANSLOCATION IN VARIOUS ADIPOSE TISSUE DEPOTS IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract. T regulatory lymphocytes (Treg) are present is adipose tissue. Their frequency, as well as the level of FoxP3 nuclear translocation, in epicardial and thymus adipose tissue remains unexplored. Properties of adipose-resident Tregs may be of high significance in patients with coronary artery disease as potential pathophysiological factor in the development of atherosclerosis. The aim of the study was to compare frequency of $FoxP3^+$Tregs and FoxP3 nuclear translocation in epicardial, thymus, subcutaneous adipose tissue and peripheral blood in patients with coronary artery disease. A pilot study was conducted in 11 patients with coronary artery disease scheduled for the coronary artery bypass graft surgery after prior selective coronary angiography. Frequency of $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes and FoxP3 nuclear translocation were evaluated by imaging flow cytometry in peripheral blood and in stromal vascular fraction of epicardial, subcutaneous and thymus adipose tissue. Frequencies of $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes were higher in epicardial adipose tissue compared to blood (3 and 5 times higher, p = 0.020); $CD4^+CD25^{lo}FoxP3^+$ cells frequency in subcutaneous adipose tissue was 4 times higher than in blood (p = 0.028). The level of FoxP3 nuclear translocation was the highest in blood and decreased in epicardial, subcutaneous and thymus adipose tissue (p = 0.020 both for $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes). Frequency of $CD4^+CD25^{lo}FoxP3^+$ cells was directly related to age in thymus (r_s = 0.818; p = 0.002), and inversely in epicardial adipose tissue (r_s = -0.618; p = 0.043). Frequencies of $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ with FoxP3 nuclear translocation in subcutaneous adipose tissue negatively correlated with age (r_s = -0.827; p = 0.002 and r_s = -0.648; p = 0.031, respectively). Frequency of $CD4^+CD25^{lo}FoxP3^+$ cells with FoxP3 nuclear translocation in thymus adipose tissue negatively correlated with waist-to-hip ratio (r_s = -0.700; p = 0.016). The severity of atherosclerosis was related only to the frequency of $CD4^+CD25^{lo}FoxP3^+$ cells in subcutaneous adipose tissue (r_s = -0.655; p = 0.029). Thus, epicardial and subcutaneous adipose tissue are enriched with Tregs, but factors that influence Treg accumulation and FoxP3 nuclear translocation in these fat depots may be different. The obtained results may further be used for personalized immunomodulatory therapy in patients with atherosclerosis.

Keywords: epicardial adipose tissue, thymus, T regulatory lymphocytes, FoxP3, subcellular localization, atherosclerosis, coronary artery disease

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Introduction

Adipose tissue plays one of the key roles in the regulation of metabolism, inflammation and endocrine functions through a finely tuned system of adipokines, chemokines, intercellular interactions both between adipocytes and between cells of the stromal vascular fraction of adipose tissue, composed of endothelial cells, pericytes, lymphocytes, monocytes, dendritic cells, and adipose-derived stromal stem cells [15]. Various fat depots have been demonstrated to possess unique properties and some of them may be directly involved in the pathogenesis of atherosclerosis. Epicardial adipose tissue (EAT) is a unique fat depot situated between the myocardium and the epicardium, and its dysfunction is associated with the development of coronary artery disease (CAD) [8]. Replacement of thymus with adipose tissue (thymus adipose tissue, TAT) takes place since young adulthood and continues throughout the lifetime. The development of atherosclerosis may be interconnected with the decline of thymus function, but the pathophysiology of this process remains unexplored [3].

T regulatory lymphocytes (Tregs) represent an important cell population in adipose tissue, regulating development of the local and systemic inflammation and maintaining insulin sensitivity in adipose tissue [15]. Decrease of adipose-resident Tregs was associated with increase of inflammatory cytokine production and adipose tissue dysregulation. Tregs in adipose tissue turned out to be primarily of thymus origin and express molecules typical to canonical Tregs, such as CD25, FoxP3, glucocorticoid-induced tumor necrosis factor receptor (GITR), cytotoxic T lymphocyte antigen-4 (CTLA-4), and OX40. The specificity of TCR-receptor was different in adipose-resident Tregs, and they appeared to be highly dependent on the activity of peroxisome proliferator-activated receptor-γ (PPAR-γ) and ST2, a receptor to IL-33 [12]. The majority of data on Tregs in adipose tissue was obtained in animal-studies and requires translation into clinics. Information on Tregs in EAT and TAT is absent.

Translocation of FoxP3 to the nucleus is an obligatory process for the stable suppressive activity of Tregs. Its perinuclear accumulation in cytoplasm was associated with the disruption of Treg regulatory functions [10]. The level of FoxP3 nuclear translocation in adipose tissue remains unexplored. The development of many autoinflammatory disorders was associated with the increase of $CD4^+CD25^{lo}FoxP3^+$ lymphocytes that presumably represent terminal differentiation stage of regulatory T cells [4]. Since atherosclerosis also represents a chronic inflammatory disorder with autoimmune component [11], one may expect increase of $CD4^+CD25^{lo}FoxP3^+$ lymphocytes during CAD as well, but their numbers have never been previously evaluated in adipose tissue of patients with CAD.

The aim of the study was to compare frequency of $FoxP3^+$Tregs in epicardial, thymus, subcutaneous adipose tissue and peripheral blood and explore FoxP3 nuclear translocation in patients with coronary artery disease.

Materials and methods

We have performed a pilot study which included 11 patients with CAD scheduled for the coronary artery bypass graft surgery (CABG) who underwent selective coronary angiography. All the procedures and tests were conducted in accordance with the guidelines of the Declaration of Helsinki and "Rules of Clinical Practice in the Russian Federation", approved by the Order of the Ministry of Health of the Russian Federation. The study's protocol was approved by the Biomedical Ethics Committee of Cardiology Research Institute, Tomsk NRMC (protocol № 210 from February 18, 2021). All patients recruited into the study signed an informed consent.

Exclusion criteria included: acute cardiovascular complications at least 6 months prior to the study (stroke, myocardial infarction, transient ischemic attack); active inflammatory disease other than atherosclerosis; chronic kidney disease class above C3b; decompensated diabetes mellitus; cancer; hematological and autoimmune disorders; change in body weight of more than 3% in the previous 3 months; refusal to participate in the study.

Anthropometric measurements were performed to assess total obesity according to the level of body mass index (BMI) and abdominal obesity according to the size of the waist circumference, hip circumference, and waist-to-hip ratio. The selective coronary coronary angiography was performed on angiographic complex Cardioscop-V and computer system Digitron-3NAC, Siemens (Germany). The severity of atherosclerosis was estimated via calculation of Gensini Score [7].

The basic characteristics of patients are presented in Table 1.

The samples of EAT, TAT and SAT were obtained in the amount 0.2-1.0 g during the CABG surgery. The samples were placed in M1999 medium preheated to 37 °C straight after obtainment and processed not later than 15 minutes after collection. To isolate the stromal-vascular fraction of adipose tissue, samples were minced, and placed into 5 mL of collagenase type I solution (PanEco, Moscow, Russia) 1 mg/mL in Krebs-Ringer buffer (2 mM D-glucose, 135 mM NaCl, 2.2 mM CaCl2·2H2O, 1.25 mM MgSO4·7H2O, 0.45 mM KH2PO4, 2.17 mM Na2HPO4, 25 mM HEPES, 3.5% BSA, 0.2 mM adenosine) at 37 °C for 35-40 minutes. Krebs-Ringer buffer (37 °C) was ad-

TABLE 1. BASIC CHARACTERISTICS OF PATIENTS

Parameter	
Sex (men/women)	10/1
Age, years	66 (58-70)
Patients with hypertension, n (%)	10 (90,9)
Hypertension duration, years	15 (10-17)
Patients with diabetes mellitus type 2, n (%)	4 (36.4)
Duration of diabetes in patients with diabetes mellitus type 2, years	10.5 (8.5-18)
Atherosclerosis severity (Gensini Score, points)	57.0 (30.5-75.0)
Body mass index, kg/m²	28.7 (24.7-31.0)
Waist circumference, cm	100 (96-111)
Waist-to-hip ratio	0.99 (0.96-1.07)
Statins intake, n (%)	9 (100)

ded to the digested tissue to neutralize collagenase in 1:1 ratio. The suspension of cells was filtered through the nylon mesh (Falcon™Cell strainer, 100 μm), adipocytes were removed, and the suspension of stromal-vascular cells was centrifuged at 400 g for 5 minutes at 4 °C, filtered through the 70 μm strainer (Falcon™Cell strainer) and centrifuged at 400 g for 5 minutes at 4 °C. The pellet was resuspended in RPMI 1640 containing 10% fetal bovine serum, 1% L-glutamine and 1% penicillin/streptomycin.

The peripheral blood mononuclear cells (PBMC) were isolated 1-2 days prior to the scheduled CABG surgery using Histopaque 1077 (Sigma Aldrich, USA).

Imaging flow cytometry was used to identify $FoxP3^+$Treg cells both in PBMC and stromal vascular fraction of adipose tissue. For this purpose, cells were stained with anti-CD45APC-Cy 7, anti-CD4 FITC, anti-CD25 PE or anti-CD25 APC (BD Pharmingen, USA). The residual erythrocytes were lysed, cells were fixed, permeabilized with a specialized buffer set (BD Pharmingen, USA) and stained with anti-FoxP3 PE or anti-FoxP3 AF647 (BD Pharmingen, USA). After intracellular staining, cells were fixed and stained with DNA dye 7-actinoaminomycin D (7-AAD, BD Pharmingen, USA).

Cells were acquired on Amnis FlowSight (Luminex, USA) equipped with 488 nm and 642 nm lasers in INSPIRE software (Amnis Corporation, Seattle, USA). Brightfield images were acquired in channel 1. Side scatter was evaluated in channel 6 using 785 nm laser. Frequencies of both $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes were evaluated. Nuclear Localization Wizard was used for analysis of FoxP3 nuclear translocation. Cell subset, positive both for 7-AAD and FoxP3 staining, was identified using inbuilt wizard algorithm, and the degree of cross-correlation between 7-AAD and FoxP3 signals was calculated based on the feature Similarity Morphology. As a result, percentages of cells with nuclear and cytoplasmic FoxP3 localization out of all FoxP3-positive cells were obtained separately for $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes.

Data were analyzed using STATISTICA 10.0 (StatSoft, USA). Shapiro-Wilks test was used for evaluation of the type of distribution of variables in the data set. Results were represented as median and interquartile interval (Me ($Q_{0.25}$-$Q_{0.75}$)). Categorical data were described by absolute (n) and relative (%) frequencies. The Mann-Whitney U-test was used to estimate the significance of differences between groups. Spearman's rank correlation coefficient (r_s) was used to estimate relationships between the variables. A value of $p < 0.05$ was considered statistically significant.

Results and discussion

We revealed that EAT had the highest frequency of $CD4^+CD25^{hi}FoxP3^+$ cells, which exceeded median values in blood by 3 times approximately, and SAT $CD4^+CD25^{hi}FoxP3^+$ cell frequency also tended to increase (Figure 1). As for $CD4^+CD25^{lo}FoxP3^+$ cells, their frequency was also the highest in EAT, exceeding peripheral blood frequency by 5 times, followed by the frequency of $CD4^+CD25^{lo}FoxP3^+$ cells in SAT, which was 4 times higher than blood median value (Figure 1). Frequencies of both $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes in TAT were comparable to the blood (Figure 1).

Frequency of $CD4^+CD25^{hi}FoxP3^+$ cells with FoxP3 nuclear translocation, on the contrary, was lower in all the studied fat depots compared to the blood (Figure 1). Of note, in TAT frequency of $CD4^+CD25^{hi}FoxP3^+$ lymphocytes was higher compared to EAT, and tended to increase compared to SAT (Figure 1). Frequency of $CD4^+CD25^{hi}FoxP3^+$ lymphocytes with FoxP3 nuclear translocation was also lower in TAT, EAT and SAT compared to blood (Figure 1).

There were no correlations between frequencies of $FoxP3^+$ cells in fat depots and $FoxP3^+$ cells in the blood. Meanwhile, the level of FoxP3 nuclear translocation in EAT correlated with the level of FoxP3 nuclear translocation in TAT in $CD4^+CD25^{hi}FoxP3^+$ lymphocytes ($r_s = 0.843$; $p = 0.001$), while the level of FoxP3 nuclear translocation in SAT correlated with the level of FoxP3 nuclear translocation in TAT in $CD4^+CD25^{lo}FoxP3^+$ lymphocytes ($r_s = 0.878$; $p < 0.001$); these indicate the common regularities of $FoxP3^+$ cell functioning in adipose tissue, and may be explained by the primarily thymus origin of adipose-resident Tregs [15]. The question remains whether $FoxP3^+$ cells in thymus adipose tissue represent newly

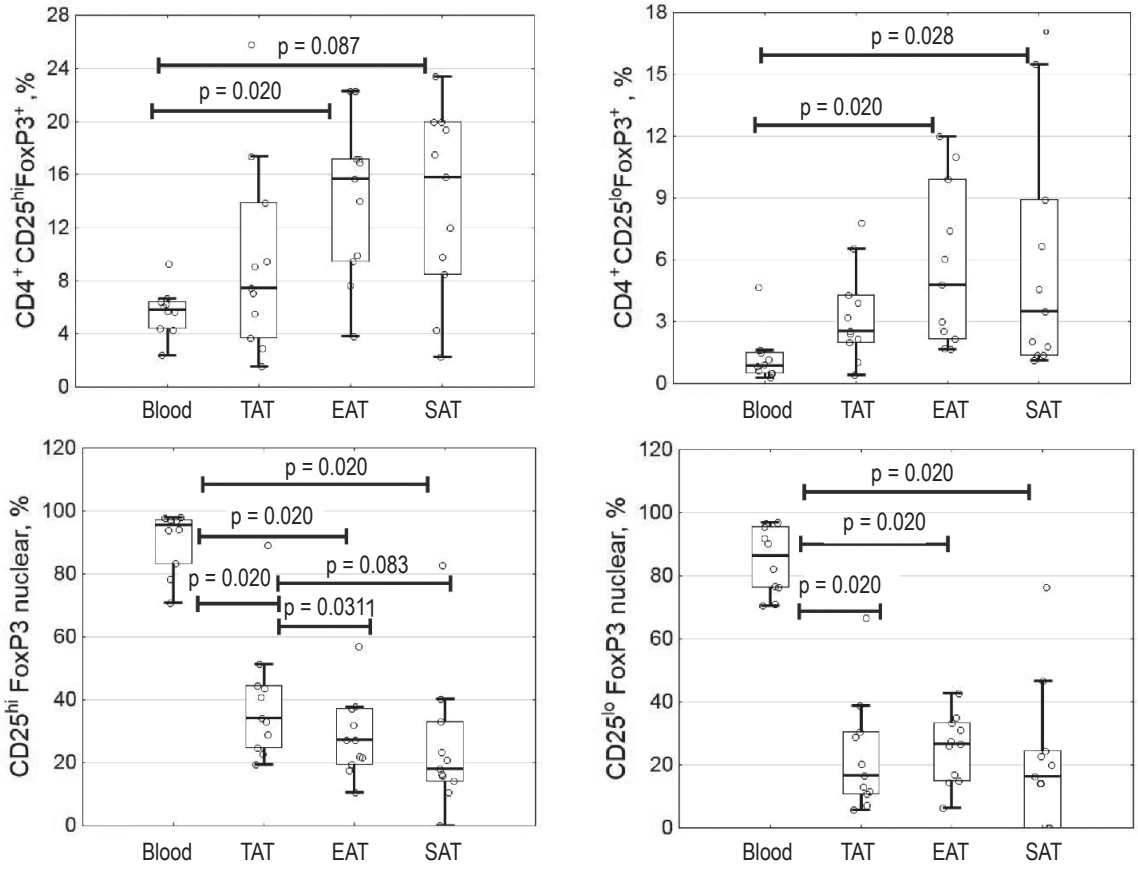

Figure 1. Frequency of T regulatory lymphocytes and frequency of cells with FoxP3 nuclear translocation in peripheral blood and various fat depots

Note. TAT, thymus adipose tissue; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; FoxP3 nuclear, cells with FoxP3 nuclear translocation; indicated p values are after Bonferroni correction.

developed thymic Tregs, or belong to the subset of recirculating Tregs, which could have migrated from the periphery and possess the capacity to suppress *de novo* Treg production [9]. Detection of other cell markers, such as CD31, that was not possible at this stage of work, will be required in future.

Since nuclear translocation of FoxP3 is obligatory for Treg suppressive function, predominant cytoplasmic localization of FoxP3 may display the decreased functional capacity of adipose-resident Treg-cells in CAD patients. However, adipose Tregs have been shown to be highly dependent on activity of PPAR-γ. In adipose tissue, PPAR-γ in conjunction with FoxP3 regulates the transcriptional activity of Treg genes, and mediates Treg responses to the metabolic changes in microenvironment [14]. Hence lower nuclear translocation of FoxP3 in adipose-resident Tregs revealed in our study may be counterbalanced by PPAR-γ activity. This hypothesis requires confirmation in further studies.

Frequency of $CD4^+CD25^{lo}FoxP3^+$ cells was directly related to age in TAT ($r_s = 0.818$; $p = 0.002$), and inversely – in EAT ($r_s = -0.618$; $p = 0.043$). In SAT, we revealed negative correlation between age and frequency of both $CD4^+CD25^{hi}FoxP3^+$ cells and $CD4^+CD25^{lo}FoxP3^+$ cells with FoxP3 nuclear translocation ($r_s = -0.827$; $p = 0.002$ and $r_s = -0.648$; $p = 0.031$, respectively) (Figure 2). The first observation that numbers of Treg cells in adipose tissue depend on age was received in mice. Increase of Tregs was observed between 5 and 25 weeks, then dropped significantly at the age of 40 weeks [2]. According to our data, age influences distribution of human $FoxP3^+$ cells among various fat depots unequivocally. Of note, we did not observe dependence of $CD4^+CD25^{hi}FoxP3^+$ cell numbers upon age, probably due to the small sample size.

Frequency of $CD4^+CD25^{lo}FoxP3^+$ cells with FoxP3 nuclear translocation in TAT negatively correlated with waist-to-hip ratio ($r_s = -0.700$; $p = 0.016$) (Figure 2). Waist-to-hip ratio represents a surrogate marker of visceral adiposity [5]. According to the findings of Yang H. et al., the degree of adiposity in thymus appeared to be inversely related

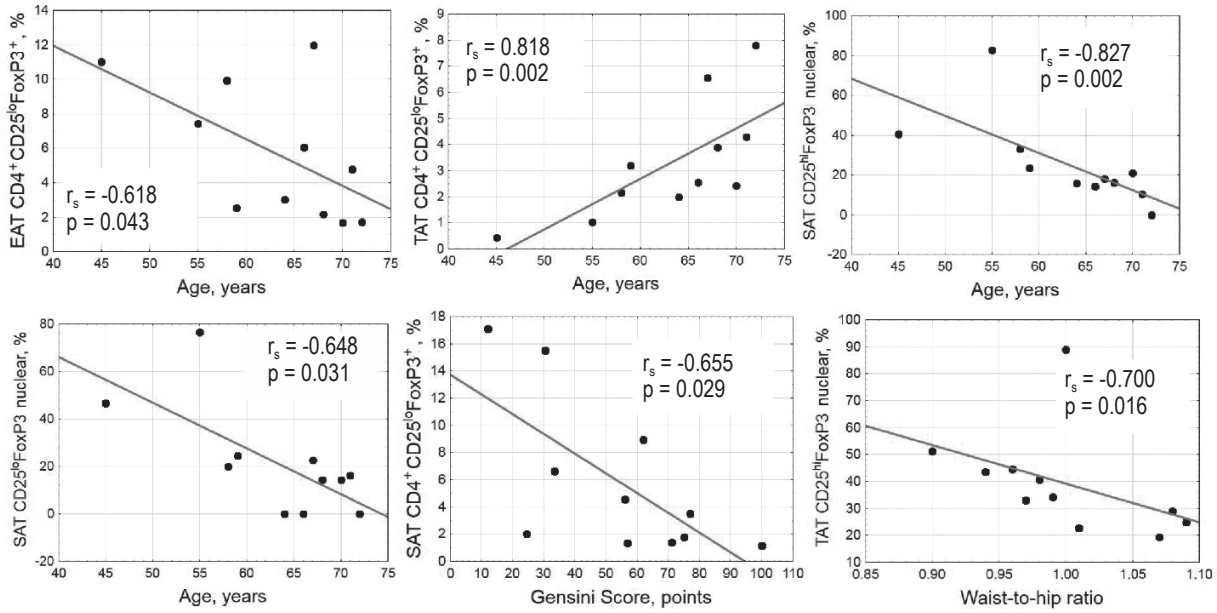

Figure 2. Correlations between basic patient characteristics and frequency of FoxP3⁺ cells in thymus, epicardial and subcutaneous fat depots

Note. TAT, thymus adipose tissue; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; FoxP3 nuclear, cells with FoxP3 nuclear translocation.

to the preservation of thymic immune function [13]. Our results support the idea that thymic regulatory potential may depend on the degree of systemic obesity as well.

The severity of atherosclerosis was related only to the frequency of $CD4^+CD25^{lo}FoxP3^+$ cells in SAT (r_s = -0.655; p = 0.029) (Figure 2). The ability of Tregs to inhibit the development of atherosclerosis have been demonstrated in multiple studies [6]. Usually, visceral or ectopic adipose tissue (such as omental, or, in our case, epicardial adipose tissue) are attributed the major significance in modulation of the cardio-metabolic health compared to subcutaneous fat [8]. Meanwhile, recently it was demonstrated that activation of NLRP3 in SAT is associated with the severity of coronary atherosclerosis and CAD development [1]. Our data indicate that Treg-lymphocytes might be involved in the development of inflammation in SAT and mediate its interconnection with the development of coronary atherosclerosis.

Conclusion

Thus, in our study we demonstrated for the first time, that epicardial and subcutaneous adipose tissues of patients with coronary artery disease are highly enriched with $CD4^+CD25^{hi}FoxP3^+$ and $CD4^+CD25^{lo}FoxP3^+$ lymphocytes, while nuclear translocation of FoxP3 in adipose-resident Tregs is diminished compared to blood. Age is an important factor of modulation of both adipose Treg frequency and the degree of FoxP3 nuclear translocation, while the severity of atherosclerosis is primarily interconnected with FoxP3 nuclear translocation in subcutaneous adipose tissue. The obtained results may further be used for personalized immunomodulatory therapy in patients with atherosclerosis.

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