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СУБКЛЕТОЧНАЯ ЛОКАЛИЗАЦИЯ ТРАНСКРИПЦИОННОГО ФАКТОРА FoxP3 У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ: СРАВНИТЕЛЬНЫЙ АНАЛИЗ И ПРОСПЕКТИВНОЕ НАБЛЮДЕНИЕ

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Резюме. Ключевые клеточные и молекулярные факторы, вовлеченные в разрешение воспаления после острого инфаркта миокарда, остаются изученными недостаточно. Т-регуляторные (Treg) лимфоциты характеризуются значительным потенциалом к регуляции силы и направления иммунных ответов при повреждении миокарда. Функциональная активность Treg-лимфоцитов зависит от транскрипционного фактора forkhead box protein P3 (FoxP3). Он также может экспрессироваться в конвенционных Т-лимфоцитах на этапе их активации. Ядерная локализация FoxP3 является обязательным условием, определяющим способность FoxP3 вносить вклад в регуляцию супрессорной активности Treg-лимфоцитов.

Целью данной работы стала сравнительная оценка частоты и абсолютного количества FoxP3$^+$Т-лимфоцитов, в сочетании с определением субклеточной локализации FoxP3, у пациентов с острым инфарктом миокарда и хроническим коронарным синдромом, а также исследование изменений этих параметров в краткосрочный период наблюдения пациентов с инфарктом миокарда. Исследование включало 14 пациентов с хроническим коронарным синдромом (8 мужчин; 6 женщин; средний возраст 63,2±9,0 лет) и 5 пациентов с острым передним инфарктом миокарда с подъемом сегмента ST (4 мужчины; 1 женщина; средний возраст 61,4±11,2 лет), обследованных на 1-е, 3-и и 7-е сутки после события. Частота FoxP3$^+$ конвенционных и регуляторных Т-лимфоцитов оценивалась во фракции мононуклеарных лейкоцитов периферической крови, наряду с определением уровня ядерной локализации FoxP3, методом проточной цитометрии с визуализацией.

Пациенты с инфарктом характеризовались снижением абсолютного количества FoxP3$^+$Treg-лимфоцитов, по сравнению с пациентами с хроническим коронарным синдромом, и демонстрировали еще более выраженное снижение абсолютного количества FoxP3$^+$Treg-клеток к 7-му дню после инфаркта, в то время как относительное количество Treg и конвенционных Т-лимфоцитов значимо не различалось. Уровень ядерной локализации FoxP3 был ниже как в Treg, так и в конвенционных Т-лимфоцитах пациентов с инфарктом в первый день, по сравнению с пациентами с хроническим коронарным синдромом. Абсолютное количество FoxP3$^+$Treg с ядерной локализацией оставалось

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значимо сниженным на 1-е и 7-е сутки после инфаркта по сравнению с пациентами с хроническим коронарным синдромом.

Таким образом, в нашем исследовании мы показали, что ядерная локализация FoxP3 снижается при остром инфаркте миокарда и может являться более чувствительным маркером изменения функционирования Treg, по сравнению с обычной оценкой их относительного количества.

Ключевые слова: FoxP3, Т-регуляторные лимфоциты, Т-конвенцинные лимфоциты, субклеточная локализация, острый коронарный синдром, хронический коронарный синдром

SUBCELLULAR LOCALIZATION OF FoxP3 TRANSCRIPTION FACTOR IN PATIENTS WITH ACUTE CORONARY SYNDROME: COMPARATIVE ANALYSIS AND PROSPECTIVE OBSERVATION

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Abstract. The key cellular and molecular factors being involved in the resolution of inflammation following acute myocardial infarction remain poorly understood. T-regulatory (Treg) lymphocytes are characterized by the extreme potential to regulate the strength and direction of immune responses during the myocardial injury. The functional activity of Treg-lymphocytes depends upon the transcription factor forkhead box protein P3 (FoxP3). It may be also expressed in conventional T-lymphocytes at the stage of their activation. Nuclear localization of FoxP3 is a prerequisite factor determining its ability to impact the suppressive functions of Treg-lymphocytes.

The aim of the present study was comparative evaluation of FoxP3$^+$T-lymphocytes frequency and counts, combined with estimation of FoxP3 subcellular localization, in patients with acute myocardial infarction and chronic coronary syndrome and examination of changes of these parameters in the short-term follow-up of patients with myocardial infarction. The study included 14 patients with chronic coronary syndrome (8 males; 6 females; 63.2±9.0 y. o.) and 5 patients with acute anterior ST-segment elevation myocardial infarction (4 males; 1 female; 61.4±11.2 y. o.) at days 1, 3 and 7 after the event. The frequency of FoxP3$^+$ conventional and regulatory T-lymphocytes was evaluated in peripheral blood mononuclear cells together with estimation of the level of FoxP3 nuclear localization by imaging flow cytometry.

Patients with infarction were characterized by the decreased counts of FoxP3$^+$Treg-lymphocytes compared to patients with chronic coronary syndrome, and exhibited even further decrease in the counts of FoxP3$^+$Treg-cells at day 7 after infarction, while frequency of Treg and conventional T-lymphocytes did not differ significantly. The level of FoxP3 nuclear translocation was lower both in Treg and conventional T-lymphocytes in patients at day 1 post-infarction compared to patients with chronic coronary syndrome. Absolute counts of FoxP3$^+$Tregs with nuclear FoxP3 localization remained significantly lower both at days 1 and 7 post-infarction compared to patients with chronic coronary syndrome.

Thus, here we demonstrated that FoxP3 nuclear localization experiences decrease in the course of acute myocardial infarction and may serve as a more sensitive marker of changes in Treg-lymphocyte functioning than simple evaluation of their frequency.

Keywords: FoxP3, T-regulatory lymphocytes, T-conventional lymphocytes, subcellular localization, acute coronary syndrome, chronic coronary syndrome

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Introduction

Even though the current therapeutic approaches allowed to make a prominent breakthrough in management of patients with acute myocardial infarction (AMI), the burden of heart failure (HF) developing further still poses the major problem worldwide. It is associated with unfavorable left ventricle remodeling following improper resolution of the post-infarct inflammation. In the course of myocardial injury the reparative phase is expected to be initiated after the day 4 post-MI. However, the key cellular and molecular factors being involved

in the regulation of shift between development of inflammation and its resolution remain obscure. T regulatory (Treg) lymphocytes represent the most perspective cellular population to impact the heart healing after AMI [7].

Treg-lymphocytes are characterized by the immense potential to regulate the magnitude and modality of immune responses during the acute myocardial injury able to suppress the activity of T-conventional (Tconv) cells, govern differentiation of macrophages towards M2 phenotype and limit recruitment of pro-inflammatory leukocytes towards the site of infarction [9, 10, 11]. A whole body of surface markers have been evaluated to distinguish Tregs among remaining $CD4^+$T-lymphocytes. Unfortunately, the majority of them have been confirmed to be unspecific. Until recently, transcription factor forkhead box protein P3 (FoxP3) was considered as a unique marker and master regulator of the Treg subset program. Later, an evidence emerged that FoxP3 may also be expressed by the Tconv-lymphocytes upon activation. However, FoxP3 in Tconv-cells was primarily confined to the cytoplasm [6].

The subcellular localization of FoxP3 holds a great importance in functioning of Treg-lymphocytes. Only upon nuclear translocation, FoxP3 is able to stabilize the transcription of the Treg-associated genes (*Ctla4, IL2ra*) and suppress transcription of the genes specific to Tconv-lymphocytes (*IFNγ, IL2* etc.). The process of nuclear translocation is rather complex, and depends on cell functional status [8]. The data on the FoxP3 subcellular localization in Treg and Tconv-lymphocytes in patients with chronic and acute coronary syndromes are unexplored.

The aim of the present study was to compare percentage and number of $FoxP3^+$T-lymphocytes along with estimation of FoxP3 subcellular localization, in patients with acute myocardial infarction and chronic coronary syndrome and examine their changes in the short-term follow-up of patients with myocardial infarction.

Materials and methods

The study was conducted at the Cardiology Research Institute of the Federal State Budgetary Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences". The protocol was approved by the local ethics committee and designed according to the principals of the Helsinki Declaration. There were enrolled 14 patients with chronic coronary syndrome (CCS) (8 males; 6 females; 63.2±9.0 y.o.) and 5 patients with acute anterior ST-segment elevation myocardial infarction (STEMI) (4 males; 1 female; 61.4±11.2 y.o.) at days 1, 3 and 7 after the onset. All the patients signed an informed consent to participate in the study.

All patients underwent selective coronary angiography on an Artis one angiographic complex and Digitron-3NAC computer system (Siemens Shenzhen Magnetic Resonance Ltd., Shenzhen, China). The severity of the atherosclerosis was assessed by calculating the Gensini Score, that, on average, was 27.5 (16.0-44.0) [3]. All CCS patients received optimal therapy. Reperfusion of the infarct-related artery (IRA) has been achieved in all STEMI patients (the mean time of recanalization constituted 5 hours), and coronary angioplasty and IRA stenting were performed. Health status was evaluated and functional class of chronic heart failure was assessed according to the 6-minute walk test. Exclusion criteria were as follows: acute coronary events earlier than 6 months before the study (transitory ischemic attack, acute coronary syndrome, acute myocardial infarction); coronary artery bypass graft earlier than 6 months prior the study; obesity class III and higher (BMI > 40); confirmed symptomatic forms of arterial hypertension; severe comorbidity (hepatic, kidney failure, oncological diseases); refusal from participation in the study.

The peripheral blood mononuclear cells (PBMCs) were obtained from the fasting heparinized blood via centrifugation on density gradient (Histopaque 1077, Sigma Aldrich, USA). $FoxP3^+$T-regulatory lymphocytes were identified among $CD4^+$-cells by high CD25 expression and detected intracellular transcription factor FoxP3. $FoxP3^+$T-conventional lymphocytes were identified among $CD4^+$-cells by low CD25 expression and detected intracellular transcription factor FoxP3. Monoclonal antibodies used were as follows: FITC-anti-CD4, APC-anti-CD25, PE-anti-FoxP3 (BD eBiosciences, USA).

After the surface staining cells were fixed and permeabilized with specific buffer solutions for detection of FoxP3 (BD eBiosciences, USA). Next, cells were incubated with PE-anti-FoxP3 antibodies. After the final wash and fixation cells were incubated with 7-Amino-Actinomycin D (7-AAD) for nuclear staining. Samples were analyzed on imaging flow cytometer AMNIS FlowSight using INSPIRE software (MD Millipore, Seattle, USA). The Nuclear Localization Wizzard was used for $CD4^+CD25^{high}$ and $CD4^+CD25^{lo}$ subsets to calculate Similarity Morphology between PE-anti-FoxP3 and 7-AAD which corresponded to the frequency of Treg and Tconv-lymphocytes with nuclear FoxP3 localization. The absolute count of $FoxP3^+$-cells was calculated by using the hemocytometer data.

Statistical analysis was performed by using Statistica 10 ("StatSoft" Inc., USA) software. The Mann–Witney U-test was used to estimate the differences between independent groups. Wilcoxon matched pairs signed rank test was used to evaluate the differences between dependent groups. Spearman's rank correlation coefficient (r) was used to estimate statistical significance between variables. Difference between groups were considered significant at level of p value below 0.05.

Results and discussion

STEMI patients on day 1 post-MI were characterized by insignificantly decreased frequency of Treg-lymphocytes and insignificantly elevated frequency of Tconv-lymphocytes compared to CCS patients (Table 1). Meanwhile, the level of FoxP3 nuclear translocation was lower both in Treg and Tconv-lymphocytes in STEMI patients on day 1 post-MI compared to CCS patients (Table 1).

We performed consecutive comparisons between the STEMI and CCS patients regarding the $FoxP3^+$-lymphocytes' frequency and the level of FoxP3 nuclear translocation during the patient follow-up. Frequency of Treg-cells insignificantly increased on day 3, while frequency of Tconv-lymphocytes insignificantly decreased (Table 1). The difference of FoxP3 nuclear translocation between STEMI and CCS patients remained on day 3, but disappeared on day 7 (Table 1).

In STEMI patients we revealed neither differences in $FoxP3^+$-cells frequency nor at the level of FoxP3 nuclear translocation at different time points which might be due to insufficient number of patients in STEMI group.

We calculated an absolute number of $FoxP3^+$T-lymphocytes and T-lymphocytes with $FoxP3^+$ nuclear translocation by using hemocytometer data. STEMI patients were characterized by decreased count of $FoxP3^+$Treg-lymphocytes compared to CCS patients, continued to further decrease on day 7 after infarction (Table 2). $FoxP3^+$Tconv-lymphocytes' counts also tended to insignificantly decrease (Table 2). The absolute count of cells with FoxP3 nuclear localization insignificantly increased by day 7 after STEMI. But

TABLE 1. SUBSETS OF $FoxP3^+$T-LYMPHOCYTES AND FoxP3 NUCLEAR TRANSLOCATION IN PATIENTS WITH CHRONIC AND ACUTE CORONARY SYNDROMES

Parameters	Patients with chronic coronary syndrome (n = 14)	Patients with acute coronary syndrome (n = 5)		
		day 1	day 3	day 7
$FoxP3^+$T-regulatory lymphocytes (Treg), %	7.2 (6.2-8.4)	6.7 (3.8-7.0) p = 0.297	7.7 (5.3-7.8) p = 0.687	7.0 (4.9-7.4) p = 0.444
$FoxP3^+$ T-conventional lymphocytes (Tconv),%	1.6 (1.3-1.8)	2.1 (1.0-2.8) p = 0.754	2.6 (1.7-2.8) p = 0.186	1.5 (1.4-2.3) p = 0.893
Treg with nuclear FoxP3 localization, %	98.2 (96.8-98.7)	74.8 (64.9-92.9) p = 0.026	82.3 (54.7-95.2) p = 0.007	92.9 (92.6-95.7) p = 0.056
Tconv with nuclear FoxP3 localization, %	88.3 (73.1-96.9)	58.7 (33.9-67.7) p = 0.034	63.6 (17.4-77.3) p = 0.026	72.2 (67.5-79.4) p = 0.087

Note. The frequency of Treg and Tconv-lymphocytes is represented as percentage of all $CD4^+$-lymphocytes; the frequency of lymphocytes with FoxP3 nuclear localization is represented as percentage of all $FoxP3^+$-lymphocytes; p indicates the level of significance compared to the group of patients with chronic coronary syndrome.

TABLE 2. ABSOLUTE COUNTS OF $FoxP3^+$T-LYMPHOCYTES AND T LYMPHOCYTES WITH $FoxP3^+$ NUCLEAR TRANSLOCATION IN STEMI PATIENTS AT DIFFERENT TIME POINTS

Parameters	CCS patients	STEMI patients		p
		day 1	day 7	
$FoxP3^+$T-regulatory lymphocytes (Treg), × 10^7/l	7.79 (5.34-9.48)	4.64 (2.49-4.83)	3.21 (2.21-3.65)	p_1 = 0.056 p_7 = 0.007 p_{1-7} = 0.043
$FoxP3^+$T-conventional lymphocytes (Tconv), × 10^7/l	1.50 (0.74-2.54)	1.46 (1.02-1.76)	1.01 (0.72-1.07)	p_1 = 0.687 p_7 = 0.156 p_{1-7} = 0.225
Treg with nuclear FoxP3 localization, × 10^7/l	7.35 (5.29-9.41)	1.00 (0.07-3.47)	3.12 (1.71-3.38)	p_1 = 0.007 p_7 = 0.010 p_{1-7} = 0.893
Tconv with nuclear FoxP3 localization, × 10^7/l	0.98 (0.57-2.46)	0.28 (0.03-0.99)	0.60 (0.52-0.73)	p_1 = 0.129 p_7 = 0.391 p_{1-7} = 0.225

Note. p_1 indicates the level of significance between CCS patients and STEMI patients at day 1; p_7 indicates the level of significance between CCS patients and STEMI patients at day 7; p_{1-7} indicates the level of significance between ATEMI patients at day 1 and day 7.

absolute counts of FoxP3$^+$Tregs with nuclear FoxP3 localization remained significantly lowered both on day 1 and day 7 post-STEMI compared to patients with CCS (Table 2).

According to the data of the correlation analysis, absolute count of the FoxP3$^+$Treg-lymphocytes on day 1 post-infarction inversely correlated with the end-systolic and end-diastolic volumes of the left ventricle both on days 3 and 7 of patient follow-up (r_s = -0.900; p = 0.037 for each correlation).

In our study we have revealed decreased absolute count of Tregs on day 1 post-STEMI compared to the CCS patients, which decreased even further on day 7, without significant change in their frequencies. Earlier, it was shown that Tregs are recruited into the heart as early as within the first day following the onset, and persist for up to 2 weeks [1]. We suppose that such changes in the absolute Treg numbers in our study are associated with their redistribution from the periphery to myocardial tissue, which leads to no changes in Treg frequencies. However, Banasal S.S. et al. (2019) found expression of pro-inflammatory cytokines and dysfunctional characteristics in expanded Tregs after AMI. Of note, FoxP3$^+$Tconv-cells and FoxP3 subcellular localization were not examined in this study [1]. It is possible that increased proinflammatory Tregs in the abovementioned study may be due to expansion of activated FoxP3$^+$Tconv-lymphocytes. The fact that echocardiographic features of the unfavorable left ventricle remodeling inversely correlated with absolute count of Treg-lymphocytes supports an existence of pro-resolving protective functions for genuine FoxP3$^+$Treg subpopulation.

To our knowledge, our study is the first to evaluate the level of FoxP3 nuclear translocation both in Treg and Tconv-lymphocytes in patients after STEMI compared to CCS patients and during the 7-day follow-up. We found decreased FoxP3 nuclear translocation on day 1 after STEMI compared to CCS patients that disappeared by day 7 after the onset. According to Magg T. et al. (2012) the nuclear translocation of FoxP3 may also be affected by the cell maturity. Thus, naïve CD45RA$^+$-cells predominantly expressed FoxP3 in the nucleus, whereas memory CD45RA$^-$-cells were characterized by the cytoplasmic FoxP3 localization [6]. Meanwhile, another study showed decreased ratio between the naïve and memory Treg-cells in non-ST-elevation myocardial infarction patients, with memory Tregs displaying impaired suppressive properties [9]. We may assume that such differences in FoxP3 nuclear localization both in Tregs and Tconv-lymphocytes may be accounted for not by the changes of its translocation level, but rather due to high number of memory T-lymphocytes entered the circulation at the onset of myocardial infarction. Also, existing FoxP3 isoforms lacking nuclear export sequences and tending to be restricted to nucleus has been described [6]. In particular, low expression of FOXP3Δ2 was associated with atherosclerotic plaque instability [5]. The possibility of FoxP3 alternative splicing in the course of STEMI should not be excluded. The question remains, whether Treg-lymphocytes with FoxP3$^+$ nuclear localization post-STEMI preserve their suppressive functions? It has been shown that interaction of FoxP3 with nuclear galectin-1 may interfere with its binding to DNA and abrogating FoxP3 suppressive activity [2].

Thus, in the present study we demonstrated that FoxP3 nuclear localization dampens in the course of STEMI and may be a more sensitive marker of altered Treg-lymphocyte functioning compared to assessing Treg frequency. Novel approaches in flow cytometry allow rather low labor-consuming approaches to evaluate this parameter. The data obtained also reveal an importance to take into consideration existence of the FoxP3$^+$ conventional T-lymphocyte subset. Further studies on the kinetics of FoxP3$^+$T-cells redistribution in humans and its impact on the course of the disease are required.

References

1. Bansal S.S., Ismahil M.A., Goel M., Zhou G., Rokosh G., Hamid T., Prabhu S.D.. Dysfunctional and proinflammatory regulatory T lymphocytes are essential for adverse cardiac remodeling in oschemic cardiomyopathy. *Circulation, 2019, Vol. 139, no. 2, pp. 206-221.*

2. Gao Y., Li X., Shu Z., Zhang K., Xue X., Li W., Hao Q., Wang Z., Zhang W., Wang S., Zeng C., Fan D., Zhang W., Zhang Y., Zhao H., Li M., Zhang C. Nuclear galectin-1-FOXP3 interaction dampens the tumor-suppressive properties of FOXP3 in breast cancer. *Cell. Death. Dis., 2018, Vol. 9, 416.* doi: 10.1038/s41419-018-0448-6.

3. Gensini G.G. A more meaningful scoring system for determining the severity of coronary heart disease. *Am. J. Cardiol., 1983, Vol. 51, no. 3, 606.* doi: 10.1016/S0002-9149(83)80105-2.

4. Hasib L., Ernerudh J., Jonasson L. Homeostatic shift and deficient function of naive and memory regulatory T cells in patients with coronary artery disease. *Eur. Heart J., 2013, Vol. 34, 4177.* doi: 10.1093/eurheartj/eht309. P4177.

5. Joly A.L., Seitz C., Liu S., Kuznetsov N.V., Gertow K., Westerberg L.S., Paulsson-Berne G., Hansson G.K., Andersson J. Alternative splicing of FOXP3 controls regulatory T cell effector functions and is associated with human atherosclerotic plaque s. *Circ. Res., 2018, Vol. 122, no. 10, pp. 1385-1394.*

6. Magg T., Mannert J., Ellwart J.W., Schmid I., Albert M.H. Subcellular localization of FOXP3 in human regulatory and nonregulatory T cells. *Eur. J. Immunol., 2012, Vol. 42, no. 6, pp. 1627-1638.*

7. Nahrendorf M., Swirski F.K. Regulating repair: regulatory T cells in myocardial infarction. *Circ. Res., 2014, Vol. 115, no. 1, pp. 7-9.*

8. Ni X., Kou W., Gu J., Wei P., Wu X., Peng H., Tao J., Yan W., Yang X., Lebid A., Park B.V., Chen Z., Tian Y., Fu J., Newman S., Wang X., Shen H., Li B., Blazar B.R., Wang X., Barbi J., Pan F., Lu L. TRAF6 directs FOXP3 localization and facilitates regulatory T-cell function through K63-linked ubiquitination. *EMBO J., 2019, Vol. 38, no. 9, e99766.* doi: 10.15252/embj.201899766.

9. Tang T.T., Yuan J., Zhu Z.F., Zhang W.C., Xiao H., Xia N., Yan X.X., Nie S.F., Liu J., Zhou S.F., Li J.J., Yao R., Liao M.Y., Tu X., Liao Y.H., Cheng X. Regulatory T cells ameliorate cardiac remodeling after myocardial infarction. *Basic Res. Cardiol., 2012, Vol. 107, no. 1, 232.* doi: 10.1007/s00395-011-0232-6.

10. Weirather J., Hofmann U.D., Beyersdorf N., Ramos G.C., Vogel B., Frey A., Ertl G., Kerkau T., Frantz S. Foxp3^{+} CD4^{+} T cells improve healing after myocardial infarction by modulating monocyte/macrophage differentiation. *Circ. Res., 2014, Vol. 115, pp. 55-67.*

11. Xia N., Jiao J., Tang T.T., Lv B.J., Lu Y.Z., Wang K.J., Zhu Z.F., Mao X.B., Nie S.F., Wang Q., Tu X., Xiao H., Liao Y.H., Shi G.P., Cheng X. Activated regulatory T-cells attenuate myocardial ischaemia/reperfusion injury through a CD39-dependent mechanism. *Clin. Sci. (Lond.), 2015, Vol. 128, pp. 679-693.*

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