ЭКСПРЕССИЯ АРГИНАЗЫ-1 И ТИРОЗИНКИНАЗЫ MER МОНОЦИТАМИ КРОВИ В ДИНАМИКЕ ФИЗИОЛОГИЧЕСКОЙ БЕРЕМЕННОСТИ

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Резюме. При беременности иммунная система матери должна сохранять толерантность к отцовским антигенам, обладая при этом способностью элиминировать патогены, что достигается ослаблением адоптивного иммунитета и активацией врожденного иммунитета, в частности моноцитов. Однако вопрос о функциональном фенотипе моноцитов, обладающих не только провоспалительной, но и противовоспалительной активностью, остается открытым. В настоящей работе методом проточной цитофлюориметрии исследована экспрессия ассоциированных с М2-фенотипом супрессорных маркеров Arg1 и MerTK в субпопуляциях моноцитов в динамике неосложненной беременности. В исследование были рекрутированы 53 беременных с неосложненной гестацией, включая 14 беременных в первом триместре, 20 – во 2-м и 19 – в 3-м триместре беременности. Группу сравнения составили 15 фертильных небеременных без отягощенного соматического анамнеза, имеющих в анамнезе не менее одних родов. Полученные результаты показали, что в группе небеременных циркулирующие Мо экспрессируют Arg1 и MerTK, и наибольшее относительное содержание $Arg1^+$ и $MerTK^+$ клеток сосредоточено в промежуточных и неклассических моноцитах. При беременности экспрессия исследуемых молекул в моноцитах достоверно возрастает. Усиление экспрессии MerTK проявляется одновременным увеличением содержания $MerTK^+$ клеток и средней интенсивности флюоресценции данного маркера; наблюдается в 1-м и 2-м триместре и регистрируется во всех трех субпопуляциях моноцитов. В то же время усиление экспрессии Arg1 проявляется либо увеличением доли $Arg1^+$ клеток, либо возрастанием плотности рецепторов, регистрируется на протяжении всей беременности, включая 3-й триместр, и максимально выражено в классических моноцитах. Между содержанием $Arg1^+$ и $MerTK^+$ клеток в промежуточных моноцитах имеется прямая корреляционная связь, которая усиливается по мере прогрессии беременности и в 3-м триместре выявляется также в классических и неклассических моноцитах. В целом, выявленное усиление экспрессии моноцитами Arg1 и MerTK

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свидетельствует о возрастании противовоспалительного потенциала моноцитов при беременности и участии моноцитов в регуляции воспалительного процесса на системном уровне. При этом особенности экспрессии Arg1 и MerTK в различных субпопуляциях моноцитов и в динамике беременности позволяют предполагать, что экспрессирующие Arg1 и MerTK моноциты могут опосредовать различные механизмы иммунной адаптации в ходе беременности.

Ключевые слова: субпопуляции моноцитов, беременность, иммунная адаптация, М2-поляризация, аргиназа-1, тирозинкиназа Mer

EXPRESSION OF ARGINASE 1 AND TYROSINE KINASE MER BY BLOOD MONOCYTES IN THE DYNAMICS OF PHYSIOLOGICAL PREGNANCY

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Abstract. During pregnancy, the maternal immune system must maintain tolerance to paternal antigens, at the same time being able to eliminate pathogens, which is achieved by the weakening of adoptive immunity and the activation of innate immunity, in particular, monocytes. However, the question about the functional phenotype of monocytes, having not only pro-inflammatory, but also anti-inflammatory activity, remains open. In the given work, we have investigated the expression of M2-associated suppressive markers Arg1 and MerTK in monocyte subpopulations during uncomplicated pregnancy. Fifty-three pregnant women with uncomplicated gestation were recruited, including 14 pregnant in the 1st trimester, 20 – in the 2nd and 19 – in the third pregnancy trimester. The comparison group consisted of 15 fertile unpregnant women without aggravated somatic anamnesis, with a history of at least one childbirth. The findings showed that in the unpregnant group circulating Mo express Arg1 and MerTK, and the most relative number of $Arg1^+$ and $MerTK^+$ cells is concentrated in intermediate and nonclassic monocytes. During pregnancy the expression of researched molecules in monocytes reliably increases. An increase in MerTK expression is manifested by a simultaneous increase in the number of $MerTK^+$ cells and the mean fluorescence intensity of this marker; it is observed in the 1st and 2nd trimesters and registered in all three monocyte subpopulations. At the same time, an increase in Arg1 expression is manifested either by an enhancement of $Arg1^+$ cells, or an increase in receptor density; it is registered throughout pregnancy, including the 3rd trimester, and is maximally expressed in classic monocytes. There is a direct correlation between the number of $Arg1^+$ and $MerTK^+$ cells in intermediate Mo, which increases with the progression of pregnancy, and in the 3rd trimester is also detected in classical and non-classical Mo. In general, the revealed increase in the expression of Arg1 and MerTK by monocytes indicates an increase in the anti-inflammatory potential of monocytes during pregnancy, and the involvement of monocytes in the regulation of the inflammatory process at the system level. Moreover, the features of Arg1 and MerTK expression in various monocyte subpopulations during pregnancy suggest that monocytes expressing Arg1 and MerTK can mediate different mechanisms of immune adaptation during pregnancy.

Keywords: monocyte subsets, pregnancy, immune adaptation, M2 polarization, arginase 1, Mer tyrosine kinase

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Introduction

Normal pregnancy requires the suppression of aggressive reaction of the maternal immune system to paternal antigens while simultaneously being able to eliminate pathogens. This, at first glance, contradictory condition is reached with the help of the fundamental reconstruction of maternal immune system, which is called immune adaptation [1]. Immune reconstruction involves the weakening of adoptive immunity and the strengthening of innate one. The suppression of lymphocyte-meditated cytotoxic and autoimmune reactions is targeted at

fetus protection. Arising deficiency of lymphocyte anti-infective protection is compensated by the activation of innate immunity cells [11], the most important of them are monocytes.

Human circulating monocytes (Mo) are represented by heterogenic population, in which by the expression of two markers (CD14 and CD16) three subpopulations are distinguished – classical (cMo; $CD14^{++}CD16^{-}$), intermediate (iMo; $CD14^{++}CD16^{+}$) and non-classical (nMo; $CD14^{+}CD16^{++}$) Mo, which represent consecutive stages of differentiation and possess different functions [3]. During pregnancy the Mo total number enhances mainly due to iMo, and these cells are characterized by the increased expression of activation markers [1, 4, 11]. Considering the fact that iMo are effective producers of anti-inflammatory cytokines and their number grows during inflammatory diseases, it was initially considered that during pregnancy Mo have pro-inflammatory phenotype [4]. However, it was later discovered that iMo can have both pro- and anti-inflammatory properties [12], and the functional phenotype depends on activating signal. For example, activation by classic way inducts pro-inflammatory (M1) phenotype, and by alternative way – anti-inflammatory (M2) one [10, 13].

Another important aspect of immune adaptation is dynamics of immune changes, by which three immunological phases of pregnancy are distinguished. Moreover, when the second one, during which the fetus grows and the maximum protection from maternal cytotoxic cells is required, is anti-inflammatory, the first and third phases, corresponding respectively to blastocyte invasion and expulsion of fetus, are inflammatory processes. The research of local immunity has shown that on the mother-fetus border an important role in inflammatory regulation is played by M2 macrophages [5]. At the same time, the question whether monocytes take part in the regulation of inflammatory reaction on the system level remains open.

We hypothesized that from beginning to end of pregnancy the pro-inflammatory activity of Mo is balanced by an increase in their regulatory (immunosuppressive / anti-inflammatory) properties, the expressiveness of which regulates the intensity of inflammation during different stages of pregnancy. To verify this hypothesis, we aimed to study the immunosuppressive / anti-inflammatory potential of various Mo subpopulations during pregnancy. As markers of the regulatory activity of Mo associated with immune-suppressive / anti-inflammatory activity was assigned to the expression of arginase 1 (Arg1) and tyrosine kinase Mer (MerTK) [9, 15]. Expression of arginase 1 (Arg1) and tyrosine kinase Mer (MerTK) was evaluated as markers of monocyte regulatory activity associated with immunosuppressive / anti-inflammatory activity.

Materials and methods

Fifty-three pregnant women with uncomplicated gestation at the age of from 18 to 41, including 14 women in the first trimester of pregnancy, 20 in the second one and 19 in the third one, took part in this research. The primigravidae in the researched group were accounted for by 37.7% (20 women), 16.9% (9 women) had high pregnancy parity (from 3 to 7). Pregnancies in the researched group went uncomplicated. Medial durations of gestation at the moment of research were correspondingly, 9, 18.3 and 38.5 weeks. The comparison group consisted of 15 fertile unpregnant women without aggravated somatic anamnesis at the age of from 23 to 42, having no less than one delivery in anamnesis. Blood collection took place on the 4-7th day of menstrual cycle. The research was carried out after obtaining written informative agreement.

Mononuclear cells (MNC) were isolated by the method of centrifugation of heparinized blood in ficoll-verografin density gradient (p = 1.078). The estimation of classical (cMo, $CD14^{++}CD16^{-}$), intermediate (iMo, $CD14^{++}CD16^{+}$) and non-classical (nMo, $CD14^{+}CD16^{++}$) monocytes was carried out by flow cytometry with the use of PerCP-, FITC- and PE-marked monoclonal anti-HLA-DR, anti-CD14 and anti-CD16 antibodies correspondingly (BD PharMingen, USA). The relative number of $MerTK^{+}$ cells in Mo subpopulations was estimated with the use of AlexaFluor 647 anti-MerTK (BioLegend) antibodies. To estimate the intracellular expression of arginase 1, the cells were treated with permeabilizing solutions (Transcription Factor Buffer Set, BD Pharmingen) and marked with APC-conjugated anti-Arg 1 antibodies (RD Systems).

The statistic processing of the results obtained was carried out using the Statistica 6.0 software package. The data are presented as median values (Me) and quartile range ($Q_{0.25}$-$Q_{0.75}$). The nonparametric Mann–Whitney U-test was used to identify significant differences in the compared parameters. Correlation analysis was performed using Spearman's rank correlation (Rs). Differences were considered significant at a significance level of $p < 0.05$.

Results and discussion

The comparison of relative number of three Mo subpopulations in the groups of unpregnant and pregnant women (Table 1) showed a significant increase in cMo in the 1st trimester and iMo in the 2nd trimester compared to unpregnant women. The proportion of nMo did not change significantly, but in the 1st and 2nd trimesters it was significantly lower than in the 3rd trimester. The highest expression of

TABLE 1. EXPRESSION OF M2-ASSOCIATED MARKERS IN SUBPOPULATIONS OF MONOCYTES IN THE DYNAMICS OF PREGNANCY

Parameter	Unpregnant	Pregnant women		
		1st trimester	2nd trimester	3rd trimester
cMo %	88 (86-90)	92 (88-93)*	91 (86.5-92.0)	88 (84-90)&
iMo %	2.9 (2-5)	3.3 (2.7-4.4)	4.9 (4.0-6.5)* &	3.9 (2.5-6.8)
nMo %	3 (2.2-4.0)	2.3 (1.5-2.9)	2.1 (2.0-2.9)	2.9 (2.5-4.9)& #
MerTK				
cMo %	50 (43-55)	70 (64-77)*	69 (55-83)*	64 (37.0-76.2)
MFI	550 (260-640)	815 (769-879)	843 (798-912)*	635 (517-750)& #
iMo %	71 (66-87)	88.5 (80-91)*	88 (74.0-91.5)*	84 (74-90)
MFI	840 (540-1107)	1129 (1037-1383)*	1351 (1130-1542)*	990 (890-1164)& #
nMo %	75 (56-88)	92 (88-93)*	86 (79.0-89.2)&	89 (56.0-92.1)
MFI	750 (550-1020)	1176 (1066-1284)*	1381 (1128-1738)*	880 (696-1030)& #
Arg 1				
cMo %	18 (15-24)	20 (17-28)	22.5 (18-28)	22 (19-33)*
MFI	605 (563-654)	805 (673-949)*	688 (652-742)*	714 (635-749)* &
iMo %	61 (48-68)	57.5 (50-66)	50.5 (39.5-60.5)	61 (44-73)
MFI	773 (753-815)	1030 (921-1206)*	850 (744-1070)	891 (854-1307)*
nMo %	74 (53-78)	68 (59-77)	63 (51.5-74.0)	77 (53-83)#
MFI	799 (756-882)	1020 (863-1184)	892 (809-996)	820 (762-1100)

Note. *, significance of differences with the unpregnant; &, with the pregnant in the 1st trimester; #, with the pregnant in the 2nd trimester (Mann–Whitney U criterion). MFI, mean fluorescence intensity.

MerTK and Arg1 in the unpregnant group was found in subpopulations of iMo and nMo. The relative number of MerTK$^+$ and Arg1$^+$ cells and the mean fluorescence intensity (MFI) of specified markers in the given subpopulations was reliably higher than in cMo. This was most pronounced in relation to Arg1$^+$ cells, the number of which in iMo (Me 61%) and nMo (Me 74%) was more than 3 times higher than their number in cMo (Me 18%).

In comparison with the control group, the expression of MerTK in Mo of pregnant women was increased. The significant increase in MerTK$^+$ cells and MFI MerTK values in the 1st trimester was registered in all subpopulations and persisted into the 2nd trimester. At the same time, in the 3rd trimester the expression of this marker decreased. So, the MFI MerTK in all Mo subpopulations were significantly lower than in the 2nd and 1st trimesters, and the relative number of MerTK$^+$ cells in all three Mo subpopulations was the same as the similar indicator of unpregnant women.

Expression of Arg1 was also found to be increased on Mo of pregnant women. However, unlike MerTK, which was elevated only in the 1st and 2nd trimesters, an increase in Arg1 expression was observed in all trimesters. In the 1st trimester we observed the significant increase in Arg1 MFI in cMo and iMo and – as a trend – in nMo. In the 2nd trimester these changes weakened a little, as evidenced by a moderate decrease in Arg1 MFI in cMo and iMo compared to the 1st trimester. The values of MFI Arg1 during these periods were still significantly higher than in the unpregnant group, however, the differences in MFI Arg1 compared to unpregnant in iMo no longer reached statistical significance.

In the 3rd trimester the increase of Arg1$^+$ cells in cMo reached statistical significance, and MFI Arg1 level in this subpopulation continued to be increased. The increase in MFI Arg1 in iMo was again statistically significant, and in nMo population, we observed the significant increase in the proportion of Arg1$^+$ cells compared to the 2nd trimester. Thus, the increase in Arg1 expression was mostly observed in the 1st and 3rd trimesters and had the highest expression in cMo subpopulation.

Analysis of a relationship between variables demonstrated that in the unpregnant group the direct correlation between MerTK$^+$ and Arg1$^+$ cells was observed in iMo population ($Rs = 0.52$; $p = 0.048$) and in nMo ($Rs = 0.49$; $p = 0.074$). In pregnant women, there was no significant relationship between the specified subpopulations in the 1st trimester, whereas in the 2nd one it was registered only in iMo ($Rs = 0.49$; $p = 0.027$), and in the 3rd one – in all three subpopulations, including cMo ($Rs = 0.49$; $p = 0.035$), iMo ($Rs = 0.69$; $p = 0.001$) and nMo ($Rs = 0.76$; $p = 0.0002$).

The adaptation of immune system during pregnancy is connected to the weakening of adoptive immune response and the compensative activation of acquired immunity cells, among which the most important part is played by Mo. However, Mo is endowed not only with an effector, but also with a regulatory function [8]. Moreover, if the pro-inflammatory properties of Mo are actively studied, then the research of Mo anti-inflammatory and immunosuppressive activity remains in the background. This prompted us to concentrate on researching Arg1 and MerTK expression – as suppressive markers – in Mo subpopulation in the dynamics of gestation.

The results obtained lead to the conclusion that Mo of fertile unpregnant women express Arg1 and MerTK, and the expression of the specified markers manifests mostly in iMo and nMo subpopulations and is minimal in cMo subpopulation. During pregnancy, the expression of MerTK and Arg1 in Mo increases. Notably, increased MerTK expression is manifested by a simultaneous enhancement in the number of $MerTK^+$ cells and MFI level; this takes place in the 1st and 2nd trimesters and is registered in all three Mo subpopulations. Unlike merTK, the increase in Arg1 expression becomes manifest either by the increase in the $Arg1^+$ cell numbers or in MFI; it is registered throughout pregnancy, including the 3rd trimester, and is maximally expressed in cMo. Thus, in spite of the fact that both markers are associated with M2 phenotype, the changes of their expression in monocytes during pregnancy have their special characteristics, in particular, they differ in expressiveness, association with subpopulation and expression dynamics.

According to literature data, the expression of arginase 1 and tyrosine kinase Mer in macrophages is associated with immunosuppressive and anti-inflammatory activity of these cells and is viewed as functional markers of M2 phenotype [2, 7]. At the same time, the data on their expression by blood monocytes and association with Mo subpopulations amounts to practically nothing. In this aspect, we have shown for the first time that MerTK and Arg1 are expressed by human circulating monocytes; the expression of these markers, especially Arg1, is considerably higher in iMo and nMo, and there is a direct correlation between the number of $MerTK^+$ and $Arg1^+$ monocytes.

Our findings have also shown for the first time, that beginning from the 1st trimester the expression of markers responsible for immune suppression and the suppression of inflammatory response in Mo is increased. Despite the fact that the immune adaptation during pregnancy is connected firstly to tolerance induction, the starting and finishing stages of pregnancy are connected to inflammatory processes, which on local level are controlled by M2 macrophages [5]. Our findings concerning the increase in expression of MerTK and Arg1 by pregnant women's circulating Mo show that monocytes / macrophages take part in the regulation of inflammatory response not only on the local level, but also on the system one. That is, typical for pregnancy moderately expressed Mo inflammatory activity [6] is controlled by the enhancing their anti-inflammatory properties.

Interesting, in our opinion, are the data on a decrease in the expression of MerTK in monocytes in the 3rd trimester with retaining high Arg1 expression. It is known that the arginase effect is connected firstly with the suppression of T cells, because arginine, metabolized by Arg1, is responsible for supporting the proliferation of T lymphocytes [7]. In its turn, MerTK has mostly an anti-inflammatory effect on the cells of innate immunity, being a negative regulator of TLR-mediated immune response [14]. Possibly, the weakening of Mo expression of MerTK in the 3rd trimester simplifies the start of inflammatory reaction necessary to prepare for childbirth. At the same time, the increased Arg1 expression restricts the functions of cytotoxic T cells, the activity of which progressively decreases during the gestation [6].

Conclusion

The enhancement of the correlation between Arg1 and MerTK in iMo during pregnancy, which we found, may indicate an increase in the proportion of cells coexpressed the specified markers, during gestation period. The appearance of such a correlation in cMo and nMo in the 3rd trimester may display the possible role of Mo expressing Arg1 and MerTK in preventing preterm labour. However, further studies are required to verify this assumption.

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