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РОЛЬ ЦИТОТОКСИЧЕСКИХ Т-ЛИМФОЦИТОВ В ПАТОГЕНЕЗЕ ПРЕЖДЕВРЕМЕННЫХ РОДОВ

Раджабова Н.Р.[1], Сотникова Н.Ю.[1, 2], Кудряшова А.В.[1], Борзова Н.Ю.[1], Малышкина А.И.[1, 2]

[1] ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ, г. Иваново, Россия
[2] ФГБОУ ВО «Ивановская государственная медицинская академия» Министерства здравоохранения РФ, г. Иваново, Россия

Резюме. В настоящее время выявлено существование широкого спектра субпопуляций $CD8^+$Т-лимфоцитов, среди которых выделяют субпопуляции наивных и эффекторных клеток, а также клеток памяти. Считается, что $CD8^+$Т-лимфоциты являются популяцией лимфоцитов, обладающей высокой цитотоксической активностью, что имеет чрезвычайное значение во время беременности. Учитывая, что каждая субпопуляция характеризуется совокупностью продуцируемых медиаторов, поверхностных и внутриклеточных маркеров, можно предположить их роль в патогенезе преждевременных родов. Это определило необходимость исследования роли наивных клеток, эффекторных клеток и клеток памяти в развитии спонтанных преждевременных родов. Данные о содержании наивных $CD8^+$-лимфоцитов в периферической крови женщин с угрожающими преждевременными родами практически отсутствуют. Установлено, что инфильтрация $CD8^+$-лимфоцитов в зоне маточно-плацентарного контакта была связана с развитием своевременных родов. Хронический хориоамнионит является наиболее распространенным состоянием при идиопатических преждевременных родах и характеризуется инфильтрацией материнских $CD8^+$Т-клеток в хориоамниотические мембраны. В настоящее время считается, что хронические воспалительные поражения плаценты представляют собой материнское антифетальное отторжение. Это послужило поводом для исследования роли этих клеток в патогенезе преждевременных родов.

Цель – установить возможный патогенетический механизм преждевременных родов у женщин с угрожающими преждевременными родами на основании выявленных особенностей дифференцировки и функциональной активности $CD8^+$-лимфоцитов на системном уровне.

Обследование женщин производилось на базе Федерального государственного бюджетного учреждения «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения России. Всего было обследовано 126 женщин, которые ретроспективно были подразделены на 2 основные группы – женщины с угрожающими преждевременными родами (n = 68), которые была подразделена на 2 подгруппы – с исходом беременности преждевременные роды (n = 30) и своевременные роды (n = 38). В группу контроля вошли 58 женщин с неосложненным течением беременности и родившие своевременно. В популяции $CD8^+$-лимфоцитов определяли содержание центральных – Tcm ($CD45RA^-CD62L^+$), претерминально-дифференциро-

Адрес для переписки:

Раджабова Наила Рустамовна
ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ
153045, Россия, г. Иваново, ул. Победы, 20.
Тел.: 8 (905) 155-67-27.
Факс: 8 (4932) 33-62-56.
E-mail: nailaradjabova@yandex.ru

Address for correspondence:

Radzhabova Naila R.
V. Gorodkov Ivanovo Research Institute of Maternity and Childhood
153045, Russian Federation, Ivanovo, Pobedy str., 20.
Phone: 7 (905) 155-67-27.
Fax: 7 (4932) 33-62-56.
E-mail: nailaradjabova@yandex.ru

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ванных – Tem (CD45RA$^-$CD62L$^-$) и терминально-дифференцированных – Temra (CD45RA$^+$CD62L$^-$) клеток памяти. Во всех популяциях клеток памяти определяли содержание клеток, внутриклеточно продуцирующих Granzyme B. Исследования проводили с помощью моноклональных антител (мАТ) методом проточной цитофлюориметрии на цитометре FACSCanto II с использованием программного обеспечения FACSDiva (Becton Dickinson, США).

Проведен анализ особенностей относительного содержания CD8$^+$-лимфоцитов в основной группе женщин в зависимости от исхода беременности. При сравнении пациенток, имеющих клинику угрожающих преждевременных родов, беременность которых завершилась преждевременно, выявлено более высокое содержание CD8$^+$-лимфоцитов, чем в группе женщин, родивших своевременно, что свидельствует о высокой стимуляции цитотоксических Т-лимфоцитов у этой группы женщин. При угрожающих преждевременных родах происходит повышение содержания в периферической крови наивных CD8$^+$-лимфоцитов. Данные о содержании наивных CD8$^+$-лимфоцитов в периферической крови женщин с угрожающими преждевременными родами практически отсутствуют. Повышение уровня CD8$^+$Tn более выражено в подгруппе женщин с благоприятным исходом беременности. Учитывая этот факт, можно предположить, что у женщин с развившимися преждевременными родами более низкий CD8$^+$ Tn связан с их усиленной дифференцировкой в эффекторные Т-лимфоциты, с последующей их миграцией в зону плацентации. Этот процесс мог определять отмеченное нами снижение уровня терминально-дифференцированных гранзим-продуцирующих CD8$^+$-лимфоцитов в подгруппе женщин с исходом беременности преждевременные роды, что совпало с литературными данными.

Ключевые слова: беременность, преждевременные роды, Т-лимфоциты

ROLE OF CYTOXIC T-LYMPHOCYTES IN THE PATHOGENESIS OF PRETERM BIRTH

Radzhabova N.R.[a], Sotnikova N.Yu.[a, b], Kudryashova A.V.[a], Borzova N.Yu.[a], Malyshkina A.I.[a, b]

[a] *V. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ivanovo, Russian Federation*
[b] *Ivanovo State Medical Academy, Ivanovo, Russian Federation*

Abstract. Currently, the existence of a wide range of subpopulations of CD8$^+$T-lymphocytes has been revealed, among which there are subpopulations of naive and effector cells, as well as memory cells. CD8$^+$T-lymphocytes are thought to be a population of lymphocytes with high cytotoxic activity, which is of extreme importance during pregnancy. Given that each subpopulation is characterized by a set of produced mediators, surface and intracellular markers, we can assume their role in the pathogenesis of preterm birth. This determined the need to investigate the role of naive cells, effector cells, and memory cells in the development of spontaneous preterm birth. Data on the content of naive CD8$^+$-lymphocytes in the peripheral blood of women with threatened preterm birth are practically absent. It was found that the infiltration of CD8$^+$-lymphocytes in the area of uteroplacental contact was associated with the development of timely delivery. Chronic chorioamnionitis is the most common condition in idiopathic preterm birth and is characterized by the infiltration of maternal CD8$^+$T-cells into the chorioamniotic membranes. Currently, it is believed that chronic inflammatory lesions of the placenta represent maternal antifetal rejection. This led to the study of the role of these cells in the pathogenesis of preterm birth. Purpose. To establish a possible pathogenetic mechanism of preterm birth in women with threatened preterm birth on the basis of the revealed features of differentiation and functional activity of CD8$^+$-lymphocytes at the systemic level

Materials and methods. The survey of women was carried out on the basis of the Federal State Budgetary Institution "V. Gorodkov Ivanovo Research Institute of Maternity and Childhood" of the Ministry of Health of the Russian Federation. A total of 126 women were examined, which were retrospectively divided into 2 main groups – women with threatened preterm birth(n = 68), which was divided into 2 subgroups – with the outcome of pregnancy preterm birth (n = 30) and timely delivery (n = 38). The control group included 58 women with uncomplicated pregnancy and who gave birth on time. In the CD8$^+$-lymphocyte population, the content of central – Tcm (CD45RA$^-$CD62L$^+$), preterminally differentiated-Tem (CD45RA$^-$CD62L$^-$) and terminally differentiated-Temra (CD45RA$^+$CD62L$^-$) memory cells was determined. In all memory cell

populations, the content of cells producing Granzyme B intracellularly was determined. The studies were performed using monoclonal antibodies (mAT) by flow cytometry on a FACSCanto II cytometer using the FACSDiva software (Becton Dickinson, USA).

The analysis of the features of the relative content of $CD8^+$-lymphocytes in the main group of women, depending on the outcome of pregnancy, was carried out. When comparing patients with a clinic of threatened preterm birth, whose pregnancy ended prematurely, a higher content of $CD8^+$-lymphocytes was revealed than in group c of women who gave birth in a timely manner, which indicates a high stimulation of cytotoxic T-lymphocytes in this group of women. With threatening preterm birth, there is an increase in the content of naive $CD8^+$-lymphocytes in the peripheral blood. Data on the content of naive $CD8^+$-lymphocytes in the peripheral blood of women with threatened preterm birth are practically absent. The increase in $CD8^+$Tn levels is more pronounced in the subgroup of women with a favorable pregnancy outcome. Given this fact, it can be assumed that in women with preterm birth, a lower $CD8^+$Tn is associated with their increased differentiation into effector T-lymphocytes with their subsequent migration to the placental zone. This process could determine the observed decrease in the level of terminally differentiated granzyme-producing $CD8^+$-lymphocytes in a subgroup of women with a pregnancy outcome of preterm birth, which coincided with the literature data.

Keywords: pregnancy, preterm birth, T-lymphocytes

Introduction

Preterm birth is of great interest to researchers around the world, as its pathogenesis remains unexplored. Since pregnancy is a process covering long-lasting development of semi-allogeneic fetus in the uterus, a unique immunological situation is established in the "mother-fetus" interface. It is well known that the placenta is not an absolute barrier to the body cells, and the results of numerous studies show that during pregnancy, fragments of chorionic villi and fetal antigens enter maternal peripheral bloodstream. This is not accompanied by a pathological response from maternal immune system, since its emerging immune adaptation at the "mother-fetus" system allows semi-allogeneic fetus avoid rejection. Of all the suspected causes associated with spontaneous preterm birth, one of the most fundamental is pathological inflammation. Most immunological studies have focused on the role of innate immunity in the mechanisms leading to preterm birth. Indeed, the stimulation of neutrophils and macrophages by administered endotoxin or the activation of invariant natural killer T-cells by alpha-galactosylceramide causes premature birth [1, 6]. However, pathological inflammation can also be mediated by T-cells, a cellular component of the adaptive immune system. In some studies, it was found that T-cell infiltration in the area of utero-placental contact (i.e., the decidual membrane) was associated with the development of timely delivery [10]. Chronic chorioamnionitis most commonly results in idiopathic preterm birth being characterized by the infiltration of maternal $CD8^+$T-cells into chorioamniotic membranes. Emerging lesion is often accompanied by aseptic inflammation associated with the infiltration of the placental basal layer by lymphocytes or plasma cells [8]. It is currently believed that chronic inflammatory lesions in the placenta represent maternal anti-fetal rejection reaction. Since the adaptation of maternal immune system is involved in the processes that ensure successful course of pregnancy, the cause of premature birth can be coupled to impaired immunological tolerance from the very beginning of pregnancy, starting with disturbed embryo implantation. Early immune disorders can lead to impaired maternal immunological tolerance and, as a result, to excessive inflammation [4]. This led to the study a role of such cells in the pathogenesis of preterm birth, and **the aim was** to uncover potential pathogenetic mechanism of preterm birth in women with threatened preterm birth on the basis of the identified features of $CD8^+$-lymphocyte differentiation and functional activity at the systemic level.

Materials and methods

The females enrolled to thye study were examined at the Federal State Budgetary Institution "V. Gorodkov Ivanovo Research Institute of Maternity and Childhood" of the Ministry of Health of the Russian Federation. A total of 126 women were examined, which were retrospectively divided into 2 main groups – women with threatened preterm birth (n = 68), which was further divided into 2 subgroups – females with differed outcome of pregnancy such as preterm birth (n = 30) and timely delivery (n = 38). The control group included 58 women with uncomplicated pregnancy, whose anamnesis was not burdened by the presence of premature birth, habitual miscarriage, late spontaneous miscarriages, finished with timely delivery. The exclusion criteria were: multiple pregnancy, severe extragenital pathology, acute/exacerbation of chronic infection and acute allergic reactions at the time of examination, preeclampsia/eclampsia, prenatal amniotic fluid leakage, placental abruption. The study material was presented by peripheral venous blood samples. In the $CD8^+$-lymphocyte population, percentage of central – Tcm ($CD45RA^-CD62L^+$), preterminally differentiated-Tem ($CD45RA^-CD62L^-$) and terminally differentiated-Temra ($CD45RA^+CD62L^-$) me-

mory cells were determined. In all memory cell populations, percentage of perforin- and granzyme B-producing cells was determined. The studies were performed using monoclonal antibodies (mAT) for flow cytometry on a "FACSCanto II" cytometer using the "FACSDiva" software ("Becton Dickinson", USA). Monoclonal antibodies anti-CD8, anti-CD45RA, anti-CD62L, anti-Perforine, anti-GranzymeB (eBioscience) were used. Cell staining and fixation were carried out by routine protocol in accordance with the manufacturer's instructions. Percentage of cells producing intracellular Granzyme B in the $CD8^+$-lymphocyte population was evaluated by using the intracellular cell staining procedure with the commercial kit "FIX & PERM cell permeabilization reagents" (Invitrogen, USA) for permeabilization of the cell membrane. Statistical and mathematical data processing was carried out by using the package of licensed programs "Microsoft Office 2013", "Statistica for Windows 12.0, StatSoftInc.", "MedCalc v7.4.4.1". The normality test of the sample data was determined using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. Here, data distribution in the studied groups differed from the normal distribution (Gauss). To assess significance of differences in the compared values between the study groups, the Mann–Whitney U-test and the Fisher exact two-tailed two-point test were used (at $p < 0.05$, the differences were considered significant). The data are presented as Me – median, indicating 25% ($Q_{0.25}$) and 75% ($Q_{0.75}$) quartile, indicating the number of studies performed in the group (n).

Results and discussion

The analysis of the obtained data showed that percentage of $CD8^+$-lymphocytes in patients with threatened preterm birth was higher than in the control group ($p = 0.000$). We also assessed percentage of $CD8^+$-lymphocytes in the main group depending on the outcome of pregnancy. While comparing patients with a clinical picture of threatened preterm birth resulting in preterm vs. term delivery, a higher level of $CD8^+$-lymphocytes was revealed (33.5 (28.5-37.7) %; 26.8 (23.1-29.7) %, $p = 0.033$). Distribution of naive $CD45RA^+CD62L^+$ (TN)-cells, central (TCM) $CD45RA^-CD62L^+$-cells, preterminally differentiated (TEM) CD45RA-$CD62L^-$-cells, and terminally differentiated (TEMRA) $CD45RA^+CD62L^-$-cells among peripheral blood cytotoxic T-lymphocytes are shown in Table 1.

In the group of women with threatened preterm birth, a high level of naive cells in the $CD8^+$-lymphocytes was revealed, compared with pregnant women in the control group ($p = 0.000$). However, no differences between these groups in percentage of central, preterminal and terminal differentiated cells were found ($p > 0.05$). In the subgroup of women with threatened preterm birth and a favorable pregnancy outcome, an increased percentage of Tn $CD8^+$-lymphocytes was observed compared to control group ($p = 0.022$). A comparison of TCM, TEM, and TEMRA levels in the groups of women with threatened preterm birth revealed no significant differences depending on the outcome of pregnancy ($p > 0.05$). Significant differences in percentage of central, preterminal and terminal differentiated cells in the subgroups of women with the outcome of pregnancy-premature and timely delivery were not revealed. ($p > 0.05$). We also analyzed the features of intracellular Granzyme B production in $CD8^+$-lymphocytes in the studied groups. There were found no significant differences in percentage of Granzyme B-producing cells in all $CD8^+$ memory cell subsets in control and main group of women with threatened preterm birth ($p > 0.05$). A comparatively analyzed percentage of Granzyme B-producing $CD8^+$TCM, $CD8^+$TEM, and $CD8^+$TEMRA-cells in a subgroup of women with pregnancy resulting in term delivery and control revealed no significant differences ($p > 0.05$ in all cases). Women with a preterm pregnancy had decreased percentage of GranzymeB-producing terminal differentiated cells, compared with women having term delivery, as well as compared with the control group ($p = 0.01$ and $p = 0.001$, respectively). No significant differences in percentage of Granzyme B-producing $CD8^+$TCM and $CD8^+$TEM between subgroups with the outcome of preterm pregnancy

TABLE 1. CONTENT OF NAIVE CELLS AND CELLS IN THE POPULATION OF $CD8^+$-LYMPHOCYTES IN THE PERIPHERAL BLOOD IN WOMEN WITH UNCOMPLICATED PREGNANCY AND WITH THREATENED PRETERM BIRTH

Indicator, %	Threatened preterm birth n = 68	Threatened preterm birth		Control group n = 58
		Preterm birth n = 30	Timely delivery n = 38	
T_N	41.35 (32.7-51.00) p = 0.001	37 (29.3-48.4)	40.7 (33.3-46.4) p = 0.022	32.9 (28.5-41.1)
T_{CM}	11.1 (8.14-15.50)	11.1 (9.0-13.5)	10.1 (7.9-14.2)	11.9 (8.7-15.3)
T_{EM}	17.4 (30.0-30.8)	22.8 (16.9-32.1)	25.9 (19.15-30.30)	25.6 (19.9-34.2)
T_{EMRA}	19 (13.4-29.6)	18.5 (14.3-30.1)	24 (16.6-30.6)	22.4 (14.6-29.6)

Note. P, the statistical significance of the differences is indicated in comparison with the indicators of the control group.

and term delivery ($p > 0.05$ in all cases). An important mechanism of immunoregulation during pregnancy is the activation of T-lymphocytes altering modality of their differentiation and functional activity [13, 14]. In most studies, increased functional activity highlighted by excessive production of granzyme B molecules in the population of cytotoxic T-lymphocytes is associated with early spontaneous miscarriage, preeclampsia, and fetal growth retardation [4]. It is known that contact with an antigen triggers a cascade of reactions promoting the differentiation of naive lymphocytes into effector cells and memory cells. Naive T-cells (TN) exert low cytotoxic activity and circulate in the maternal body seeking out for antigens, detection of which elicits T-cell differentiation into effector cells migrating to inflammatory or alloimmune tissues [3]. A number of studies revealed that effector T-cells are present in the area of utero-placental contact (decidual membrane). It is proved that they are involved in the development of term delivery in physiologically occurring pregnancy [10, 13]. Virtually no data on percentage of naive $CD8^+$-lymphocytes in the peripheral blood of women with threatened preterm birth are available. This accounted for the need to investigate a role of naive cells, effector cells, and memory cells in the development of spontaneous preterm birth. According to our study, threatened preterm birth is coupled to increased percentage of naive $CD8^+$-lymphocytes in the peripheral blood. Due to the fact that partial thymus involution as a natural process occurs during pregnancy, we are unable to unambiguously conclude about the nature of differentiation of naive $CD8^+$-lymphocytes in threatened preterm labor (thymic/extrathymic). The most likely factors stimulating the differentiation of naive cytotoxic T-lymphocytes are the expression of specific HLA antigens, as well as the particles of cytotrophoblast cells entering the maternal bloodstream in early pregnancy [4]. Thus, recent studies have shown that fetal T-cells are activated in different subgroups of preterm labor and can cause various inflammatory reactions in the amniotic cavity, leading to preterm birth [5]. The level of such particles increases with all complications of the gestational process. The increase in $CD8^+$Tn levels is more pronounced in the subgroup of women with a favorable pregnancy outcome. Given that, it can be assumed that in women with preterm birth, a lower $CD8^+$TN is associated with their increased differentiation into effector T-lymphocytes and their subsequent migration to the placental zone. This process could determine the observed decrease in the level of terminally differentiated granzyme-producing $CD8^+$-lymphocytes in a subgroup of women with a preterm birth. In some studies, it has been shown that percentage of effector $CD8^+$ memory cells increase in the decidual membrane during spontaneous preterm birth [7]. Few data on the mechanisms of migration of $CD8^+$T-lymphocytes to the placenta are available. However, several specific molecules can be identified, the expression of which can contribute to the selective migration of cytotoxic lymphocytes into the placenta and amniotic fluid. According to the publications, decidual stromal cells express CXCR3 ligands, produce CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC), and $CD8^+$-cells are characterized by increased expression of CXCR3 and CCR5 in threatened preterm labor [11]. $CD8^+$T-cell migration may be facilitated by the expression of CXCL9 in the placenta and in the chorioamniotic membrane [9]. Increased production of this chemokine in the placenta and fetal membranes was observed in preterm labor. In addition, preterm birth was associated with an increased content of CXCL11 in the amniotic fluid during the second trimester of pregnancy [2, 12].

Thus, in the peripheral blood of women with threatened preterm birth, there is an increased differentiation of naive $CD8^+$-lymphocytes, which in the group of women with an unfavorable outcome of pregnancy such as preterm birth, is accompanied with decreased level of terminally differentiated cells with high cytotoxic potential. Perhaps, such changes result from excessive fetal antigen-cell stimulation and subsequent migration to the placenta and amniotic fluid, inducing premature birth.

References

1. Arenas-Hernandez M., Romero R., St. Louis D., Hassan S.S., Kaye E.B., Gomez-Lopez N. An imbalance between innate and adaptive immune cells at the maternal-fetal interface occurs prior to endotoxin-induced preterm birth. *Cell. Mol. Immunol., 2016, Vol. 13, pp. 462-473.*

2. Bhatti G., Romero R., Rice G.E., Fitzgerald W., Pacora P., Gomez-Lopez N., Kavdia M., Tarca A.L., Margolis L. Compartmentalized profiling of amniotic fluid cytokines in women with preterm labor. *PLoS One, 2020, Vol. 15, no. 1, e0227881.* doi:10.1371/journal.pone.0227881.

3. Brummelman J., Pilipow K., Lugli E. The Single-cell phenotypic identity of human $CD8^+$ and $CD4^+$ T Cells. *Int. Rev.Cell Mol. Biol., 2018, Vol. 341, pp. 63-124.*

4. Du M.R., Guo P.-F., Piao H.-L., Wang S.-C., Sun C., Jin L.-P., Tao Y., Li Y.-H., Zhang D., Zhu R., Fu Q., Li D.-J. Embryonic trophoblasts induce decidual regulatory T cell differentiation and maternal–fetal tolerance through thymic stromal lymphopoietin instructing dendritic cells. *J. Immunol., 2014, Vol. 192, no. 4, pp. 1502-1511.*

5. Frascoli M., Coniglio L., Witt R., Jeanty C., Fleck-Derderian S., Myers D.E., Lee T.H., Keating S., Busch M.P., Norris P.J., Tang Q., Cruz G., Barcellos L.F., Gomez-Lopez N., Romero R., MacKenzie T.C. Alloreactive fetal T

cells promote uterine contractility in preterm labor via IFN-γ and TNF-α. *Sci. Transl. Med., 2018, Vol. 10, no. 438, eaan2263.* doi: 10.1126/scitranslmed.aan2263.

6. Gomez-Lopez N., Romero R., Arenas-Hernandez M., Schwenkel G., St. Louis D., Hassan S.S., Mial T.N. *In vivo* activation of invariant natural killer T cells induces systemic and local alterations in T-cell subsets prior to preterm birth. *Clin. Exp. Immunol., 2017, Vol. 189, pp. 211-225.*

7. Gomez-Lopez N., Romero R., Panaitescu B., Leng Y., Xu Y., Tarca A.L., Faro J., Pacora P., Hassan S.S, Hsu C.-D. Inéammasome activation during spontaneous preterm labor with intra-amniotic infection or sterile intra-amniotic inéammation. *J. Perinat. Med., 2020, Vol. 48, no. 3, pp. 222-233.*

8. Kim C.J., Romero R., Chaemsaithong P., Kim J.-S. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am. J. Obstet. Gynecol., 2015, Vol. 213, no. 4 Suppl., pp. S53-S69.*

9. Maymon E., Romero R., Bhatti G., Chaemsaithong P., Gomez-Lopez N., Panaitescu B., Chaiyasit N., Pacora P., Dong Z., Hassan S.S., Erez O. Chronic inflammatory lesions of the placenta are associated with an up-regulation of amniotic fluid CXCR3: A marker of allograft rejection. *J. Perinat. Med., 2018, Vol. 46, no. 2, pp. 123-137.*

10. Pique-Regi, R., Romero, R., Tarca, A. L., Sendler, E. D., Xu, Y., Garcia-Flores, V., Leng Y., Luca F., Hassan S.S., Gomez-Lopez N. Single cell transcriptional signatures of the human placenta in term and preterm parturition. *Elife, 2019, Vol. 8, e52004.* doi: 10.7554/eLife.52004.

11. Romero R., Chaemsaithong P., Chaiyasit N., Docheva N., Dong Z., Kim C.J., Kim Y.M., Kim J.-S., Qureshi F., Jacques S.M., Yoon B.H., Chaiworapongsa T., Yeo L., Hassan S.S., Erez O., Korzeniewski S.J. CXCL10 and IL-6: Markers of two different forms of intra-amniotic inflammation in preterm labor. *Am. J. Reprod. Immunol., 2017, Vol. 78, no. 1, e12685.* doi: 10.1111/aji.12685.

12. van Egmond A., van der Keur C., Swings G.M.J.S., Scherjon S.A., F.H. J. Claas 2. The possible role of virus-specific $CD8^+$ memory T cells in decidual tissue. *J. Reprod. Immunol., 2016, Vol. 113, pp. 1-8.*

13. van der Zwan A., Bi K., Norwitz E.R., Crespo Â.C., Claas F.H., Strominger, J.L., Tilburgs, T. Mixed signature of activation and dysfunction allows human decidual $CD8^+$ T cells to provide both tolerance and immunity. *Proc. Natl Acad. Sci., 2018, Vol. 115, no. 2, pp. 385-390.*

14. Voskoboinik I., Whisstock J.C., Trapani J.A. Perforin and granzymes: function, dysfunction and human pathology. *Nat. Rev. Immunol., 2015, Vol. 15, no. 6, pp. 388-400.*

Авторы:

Раджабова Н.Р. *— аспирант кафедры акушерства и гинекологии, неонатологии, анестезиологии и реаниматологии ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ, г. Иваново, Россия*

Кудряшова А.В. *— д.б.н., старший научный сотрудник лаборатории клинической иммунологии ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ, г. Иваново, Россия*

Сотникова Н.Ю. *— д.м.н., профессор, заведующая лабораторией клинической иммунологии ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ; профессор кафедры патофизиологии и иммунологии ФГБОУ ВО «Ивановская государственная медицинская академия» Министерства здравоохранения РФ, г. Иваново, Россия*

Борзова Н.Ю. *— д.м.н., профессор, главный научный сотрудник отдела акушерства и гинекологии ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ, г. Иваново, Россия*

Малышкина А.И. *— д.м.н., профессор, директор ФГБУ «Ивановский научно-исследовательский институт материнства и детства имени В.Н. Городкова» Министерства здравоохранения РФ; заведующая кафедрой акушерства и гинекологии, медицинской генетики ФГБОУ ВО «Ивановская государственная медицинская академия» Министерства здравоохранения РФ, г. Иваново, Россия*

Authors:

Radzhabova N.R., *Postgraduate Student, Department of Obstetrics and Gynecology, Neonatology, Anesthesiology, V. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ivanovo, Russian Federation*

Kudryashova A.V., *PhD, MD (Biology), Chief Research Associate, Laboratory of Clinical Immunology, V. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ivanovo, Russian Federation*

Sotnikova N.Yu., *PhD, MD (Medicine), Professor, Head, Laboratory of Clinical Immunology, V. Gorodkov Ivanovo Research Institute of Maternity and Childhood; Professor, Department of Pathophysiology and Immunology, Ivanovo State Medical Academy, Ivanovo, Russian Federation*

Borzova N.Yu., *PhD, MD (Medicine), Professor, Chief Research Associate, Department of Obstetrics and Gynecology, V. Gorodkov Ivanovo Research Institute of Maternity and Childhood, Ivanovo, Russian Federation*

Malyshkina A.I., *PhD, MD (Medicine), Professor, Director, V. Gorodkov Ivanovo Research Institute of Maternity and Childhood; Head, Department of Obstetrics and Gynecology, Medical Genetics, Ivanovo State Medical Academy, Ivanovo, Russian Federation*

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