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ФЕНОТИПИЧЕСКИЙ ПРОФИЛЬ NK-КЛЕТОК ПЕРИФЕРИЧЕСКОЙ КРОВИ В УСЛОВИЯХ КУЛЬТИВИРОВАНИЯ С КЛЕТКАМИ ТРОФОБЛАСТА И ЦИТОКИНАМИ IL-15 И IL-18

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Резюме. Естественные киллеры (NK-клетки) являются лимфоцитами врожденного иммунитета. Дифференцировка NK-клеток находится под контролем клеток микроокружения и продуцируемых ими цитокинов, в том числе IL-2, IL-15 и IL-18. NK-клетки представлены в различных тканях, где они формируют пулы тканерезидентных естественных киллеров, одним из таких пулов являются NK-клетки децидуальной оболочки. Предполагаемым источником клеток для дифференцировки NK-клеток децидуальной оболочки являются NK-клетки периферической крови (pNK). В матке NK-клетки контактируют с клетками трофобласта, что может влиять на их фенотип. Вклад клеток трофобласта и цитокинов IL-2, IL-15 и IL-18 в регуляцию фенотипа pNK-клеток недостаточно изучен. В связи с этим целью работы была оценка влияния клеток трофобласта на фенотип pNK-клеток в условиях культивирования в среде с IL-2, IL-15, IL-18. В работе использовали мононуклеары, полученные из периферической крови здоровых небеременных женщин репродуктивного возраста, с регулярным менструальным циклом (n = 21). Мононуклеары культивировали в присутствии IL-2 и одного из цитокинов, регулирующих дифференцировку NK-клеток – IL-15 или IL-18. В качестве клеток трофобласта использовали клетки линии JEG-3. Оценивали экспрессию pNK-клетками рецепторов CD45, CD3, CD56, CD14, KIR3DL1, KIR2DL3, KIR2DL4, KIR2DS4, NKp44, CD215, CD122, CD127, NKG2D, KIR2DL1, NKG2C. Установлено, для pNK-клеток, прокультивированных в присутствии клеток трофобласта линии Jeg-3, характерна более низкая интенсивность экспрессии рецептора CD56 по сравнению с pNK-клетками, прокультивированными без клеток трофобласта. Эти изменения выявлены в случае культивирования как в среде с IL-15, так и в среде с IL-18. Выявлено сниженное количество $NKG2C^+$ pNK-клеток в присутствии клеток трофобласта линии Jeg-3 по

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сравнению с NK-клетками, прокультивированными без клеток трофобласта, при культивировании в среде с IL-15. Выявленные изменения экспрессии CD56 и NKG2C pNK-клетками в присутствии клеток трофобласта противоположны ранее установленным для NK-клеток линии NK-92. Вероятно, помимо клеток трофобласта, моноциты, присутствующие в составе мононуклеаров, под действием цитокинов, могут влиять на фенотип pNK-клеток в использованной модельной системе. Так как моноциты/макрофаги присутствуют в децидуальной оболочке, требуются дальнейшие исследования влияния цитокинов и клеток микроокружения, в том числе моноцитов, на pNK-клетки.

Ключевые слова: NK-клетки, периферическая кровь, трофобласт, IL-15, IL-18, фенотип, CD56

PHENOTYPIC PROFILE OF PERIPHERAL BLOOD NK CELLS UNDER CULTURING WITH TROPHOBLAST CELLS AND IL-15 AND IL-18 CYTOKINES

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Abstract. Natural killer cells (NK cells) are innate immunity lymphocytes. NK cell differentiation is controlled by the cellular microenvironment and locally produced cytokines, including IL-2, IL-15 and IL-18. NK cells are present in various tissues, forming pools of tissue-resident NK cells, e.g., decidual NK cell pool. Peripheral blood NK cells (pNK cells) are considered a supposed source of cells for decidual NK cell differentiation. In the uterus, NK cells contact with trophoblast cells, which can affect their phenotype. Contribution of trophoblast cells and IL-2, IL-15 and IL-18 cytokines to the pNK cell phenotype regulation is scarcely studied. In this regard, the aim of our research was to evaluate the effect of trophoblast cells on the phenotype of pNK cells when cultured in medium with IL-2, IL-15, and IL-18. We used mononuclear cells obtained from peripheral blood of healthy non-pregnant women at their reproductive age, with regular menstrual cycle (n = 21). Mononuclear cells were cultured in presence of IL-2, and either of cytokines regulating NK cell differentiation (IL-15, or IL-18). JEG-3 cells were used as trophoblast cells. We evaluated expression of CD45, CD3, CD56, CD14, KIR3DL1, KIR2DL3, KIR2DL4, KIR2DS4, NKp44, CD215, CD122, CD127, NKG2D, KIR2DL1, NKG2C receptors by pNK cells. It was found that pNK cells cultured in presence of trophoblast cells (JEG-3 cell line) were characterized by lower intensity of CD56 receptor expression, compared to pNK cells cultured without trophoblast cells. These changes were detected upon culturing both in medium supplied by IL-15, and with IL-18. A reduced number of NKG2C$^+$ pNK cells was detected in presence of JEG-3 trophoblast cells, compared to NK cells cultured without trophoblast cells in medium with IL-15. The detected changes in the CD56 and NKG2C expression by pNK cells in presence of trophoblast cells proved to be opposite to those previously detected for NK cells derived from NK-92 cell line. Along with trophoblast cells, the monocytes isolated among mononuclear cells and being affected by cytokines, can apparently influence the phenotype of pNK cells in the model system used. Since monocytes/macrophages are present in decidua, further research is required to study the effect of cytokines and cellular microenvironment, including monocytes, on pNK cells.

Keywords: NK cells, peripheral blood, trophoblast, IL-15, IL-18, phenotype, CD56

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Introduction

Natural killer cells (NK cells) are innate immunity lymphocytes. They are present in the composition of mononuclear cells of the peripheral blood making up to 15% of all lymphoid cells [1]. The differentiation

of NK cells is controlled by the cellular microenvironment and cytokines produced by it, including IL-2, IL-15 and IL-18 [15]. The IL-2 cytokine is an important growth factor for NK cells, since it stimulates their proliferation [14]. The IL-15 cytokine is produced by hematopoietic, dendritic and stromal cells, as well as by monocytes and macrophages. In the course of experiments on a mouse model with IL-15 gene knockout or without receptors to it, a decrease in the number of NK cells could be observed, while the transplantation of donor NK cells led to the death of NK cells in the absence of exogenous IL-15 [7]. The IL-18 cytokine is constitutively produced by dendritic cells, macrophages, neutrophils and epithelial cells [15]. Experiments on a mouse model showed that IL-18 stimulated the expression of IL-2R by NK cells and enhanced the proliferation of NK cells caused by IL-2 [3]. The use of IL-2, IL-15 and IL-18 cytokine combination in the culturing of peripheral blood NK cells (pNK cells) leads to the increase in their number, their cytotoxicity and their expression of CD16 and NKG2D activation receptors [9].

NK cells are present in various tissues, where they form pools of tissue resident NK cells. One of such populations of tissue resident NK cells is formed by decidual NK cells. Decidual NK cells contain lytic granules and express receptors for the molecules of the main histocompatibility complex. However, they do not exhibit a pronounced cytotoxic activity [5]. Their role in the processes of blastocyst implantation and placenta development has been proved [6]. One of the possible sources of decidual NK cells are NK cells migrating from the peripheral blood (pNK) [7]. In the uterus, NK cells come into contact with trophoblast cells, which can affect their phenotype. Cytokines IL-15 and IL-18 are present in the uteroplacental complex and can affect uterine NK cells [8, 13]. The contribution of cellular microenvironment of the decidua and cytokines IL-15 and IL-18 to pNK cell phenotype regulation has not been sufficiently studied. In this regard, **the aim of the research** was to evaluate the effect of trophoblast cells on the phenotype of pNK cells when cultured in medium with IL-2, IL-15, and IL-18.

Materials and methods

Mononuclear cells were obtained from the peripheral blood of healthy nonpregnant women of reproductive age with a regular menstrual cycle (n = 21). The exclusion criteria included acute inflammatory diseases, exacerbations of chronic diseases and intake of combined oral contraceptive pills. The average age of the women involved in the research was 29.2±6 years. Cells of the JEG-3 cell line (ATCC, USA) similar in their characteristics to extravillous trophoblast cells of the first trimester of pregnancy were used as trophoblast cells [17].

Trophoblast cells of the JEG-3 cell line (ATCC, USA) were placed in a 96-well flat bottom plate at a concentration of 20,000 cells in 100 μL a complete cell culture medium (DMEM) (Biolot, Russia). After 24 hours, mononuclear cells were isolated from the peripheral blood by centrifugation in Ficoll solution gradient (density 1.077; BioloT, Russia). The culture medium was removed from the plate wells. Mononuclear cells were then added either to trophoblast cells or to empty wells at a concentration of 100,000 cells in 100 μL of a complete cell culture medium (DMEM). IL-2 (200 U/mL) was added to all wells; IL-18 (10 ng/mL) or IL-15 (10 ng/mL) (Sigma Aldrich, USA) were added to some of the wells, thus obtaining combinations of IL-2^+/IL-15^+ and IL-2^+/IL-18^+. The cells were then incubated for 96 hours in a humid environment at 37 °C, 5% CO_2. After incubation the plate was centrifuged for 5 minutes at 200 g and 22 °C, after which the culture medium was removed from the wells, 100 μL of Versene solution (BioloT, Russia) was added to each well, and the cells were then resuspended. After that, the cells were centrifuged for 5 minutes at 200 g and 22 °C, the Versene solution was removed, and the cells were re-washed in Hanks solution by centrifugation (5 minutes at 200 g, 22 °C). Then the cells were sequentially treated with Fc receptor blocking reagent (MACS, Germany) and monoclonal antibodies to CD45, CD3, CD56, CD14, KIR3DL1, KIR2DL3, KIR2DL4, KIR2DS4, NKp44, CD215, CD122, CD127, NKG2D (BD, USA), KIR2DL1, NKG2C (R&D, USA) receptors according to manufacturers' protocol. The cell death was evaluated after culturing by treatment with 7-Amino-Actinomycin D (7-AAD). It was no more than 2% (BioLegend, USA). Isotypic antibodies (BD, USA and R&D, USA) were used to control the nonspecific binding. Cells untreated with monoclonal antibodies served as negative controls. The expression of receptors was evaluated using a FACSCanto II flow cytofluorimeter (BD, USA).

The obtained data were analyzed using the GraphPad Prism 8 software, descriptive statistics methods and nonparametric Wilcoxon test. The differences were recognized as significant at $p < 0.01$.

Results and discussion

It was found that pNK cells cultured in the presence of trophoblast cells of the JEG-3 cell line were characterized by a lower intensity of CD56 receptor expression compared to pNK cells cultured without trophoblast cells. These changes were detected both under culturing in IL-2^+/IL-15^+ medium (Figure 1A) and under culturing in IL-2^+/IL-18^+ medium (Figure 2A). A reduced number of NKG2C$^+$ pNK cells was detected in the presence of trophoblast cells of the JEG-3 cell line compared to NK cells cultured without trophoblast cells in IL-2^+/IL-15^+ medium

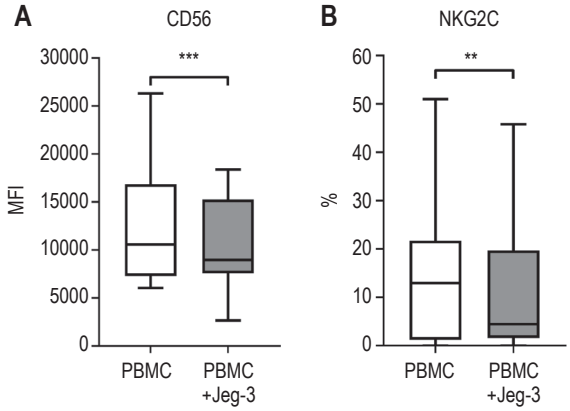

Figure 1. Receptors of pNK cells after culturing in IL-2$^+$/IL-15$^+$ medium without and with trophoblast cells of the JEG-3 cell line

Note. (A) Intensity of CD56 expression. (B) Number of NKG2C$^+$ NK cells. The significance of the differences: **, p < 0.01; ***, p < 0.001.

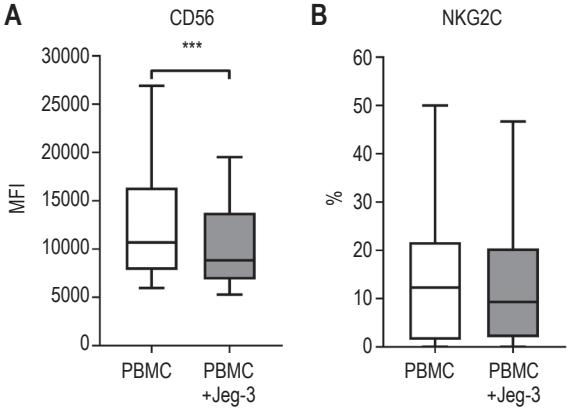

Figure 2. Receptors of pNK cells after culturing in IL-2$^+$/IL-18$^+$ medium without and with trophoblast cells of the JEG-3 cell line

Note. (A) Intensity of CD56 expression. (B) Number of NKG2C$^+$ NK cells. The significance of the differences: ***, p < 0.001.

(Figure 1B). The number of NKG2C$^+$ pNK cells did not change in the presence of JEG-3 cells when cultured in IL-2$^+$/IL-18$^+$ medium (Figure 2B).

There were no differences in the expression of KIR3DL1, KIR2DL1, KIR2DL3, KIR2DL4, KIR2DS4, NKp44, CD215, CD122, CD127, NKG2D receptors under culturing with and without JEG-3 cells in IL-2$^+$/IL-15$^+$ и IL-2$^+$/IL-18$^+$ media.

We have previously shown that culturing of NK-92 cells with trophoblast cells of the JEG-3 cell line and IL-2 stimulated the expression of CD56 and NKG2C receptors [10]. Within the system using NK-92 cells, the addition of IL-15 or IL-18 to the culture medium did not change the effect of trophoblast cells of the JEG-3 cell line on CD56 expression by NK cells [10]. While working with pNK cells, we detected an opposite change in the expression of these receptors, compared to that in the system using NK-92 cells. These differences are apparently related to the presence of not only pNK cells, but also monocytes and other lymphocytes in the composition of the mononuclear fraction in our model system.

The number of both NK cells and macrophages increases in the endometrium during the secretory phase of the cycle [5]. In the first trimester of pregnancy, M1 macrophages present in the decidua participate in the regulation of trophoblast cell invasion on an equal basis with NK cells [5]. Decidual macrophages of the first trimester of pregnancy secrete IL-12 [5]. In addition, macrophages expressing the β chain of IL-15 receptor (CD122) were described, which are also present in the decidua [4]. Under the influence of IL-15, CD122$^+$ macrophages produce TNFα and IL-6 [4]. Thus, as a result of the addition of IL-15 to mononuclear cells and their culturing in the presence of trophoblast cells, monocytes can acquire a specific secretory profile. In turn, monocyte activity modified by cytokines can stimulate changes in NK cell phenotype, in particular, it can cause a decrease in CD56 expression and in the number of NKG2C$^+$ NK cells in the presence of trophoblast cells.

The literature describes the ability of NK cells to form NK cells similar to memory cells (adaptive (aNK) cells) as a result of culturing with IL-15, IL-12 and subsequent stimulation by target cells of the K562 cell line [12]. Since peripheral blood monocytes can produce IL-12 without prior stimulation [1], it is possible for pNK cells to partially acquire adaptive characteristics. However, CD57$^+$NKG2C$^+$ phenotype has been assigned specifically for aNK cells, while CD57-CD56dim NKG2C$^+$ NK cells are possible precursors of aNK cells [6]. Earlier, using a similar model of mononuclear cell culturing in the presence of trophoblast cells of the JEG-3 cell line, we showed an increase in the number of CD16$^+$CD57bright pNK cells compared to their number before culturing [11]. At the same time, in this research, we detected a reduced number of NKG2C$^+$ NK cells when cultured in IL-2$^+$/IL-15$^+$ medium in the presence of trophoblast cells. Thus, the changes detected by us in the phenotype of pNK cells in the presence of trophoblast cells of the JEG-3 cell line and IL-15 lines do not allow us to draw a clear conclusion about aNK cell differentiation. Further studies of the effect of cytokines and trophoblast cells on pNK cells are required.

When using IL-2$^+$/IL-18$^+$ medium, we detected a decrease in the expression of CD56 by pNK cells, while the number of NKG2C$^+$ pNK cells did not

change. According to the literature, peripheral blood monocytes do not produce IL-15 in the absence of stimulation [1]. IL-18 does not cause the production of IL-15 and IL-12 by peripheral blood monocytes, but it stimulates the expression of TLR4 and secretion of TNFα and IL-10 by them [2]. This profile of cytokine secretion does not allow us to unambiguously attribute these monocytes to M1 or M2 type. In the absence of IL-15, monocytes do not apparently acquire the characteristics typical of decidual macrophages (M1 or $CD122^{+}$). Therefore, the detected decrease in the expression of CD56 by NK cells in the presence of IL-18 can be attributed to the influence of monocytes activated by IL-18, but not to the in vitro interaction between NK cells and uterine monocytes/macrophages.

Conclusion

The research detected a decrease in the intensity of CD56 expression by pNK cells as a result of simultaneous effect of IL-15/IL-18 and trophoblast cells on pNK cells in the mononuclear fraction. The established change may be associated with the presence of monocytes in the model system and their indirect effect on pNK cells.

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