ПРЕПАРАТЫ ИММУНОГЛОБУЛИНОВ ДЛЯ ВНУТРИВЕННОГО ВВЕДЕНИЯ И РЕКОМБИНАНТНОГО ГРАНУЛОЦИТАРНОГО КОЛОНИЕСТИМУЛИРУЮЩЕГО ФАКТОРА ВЛИЯЮТ НА ЭКСПРЕССИЮ ЦИТОТОКСИЧЕСКИХ РЕЦЕПТОРОВ NK-КЛЕТОК

Давыдова А.А., Михайлова В.А., Ковалева А.А., Гребенкина П.В., Тыщук Е.В., Зементова М.С., Беспалова О.Н., Соколов Д.И., Сельков С.А.

ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия

Резюме. Естественные киллеры (NK-клетки) представляют собой популяцию лимфоцитов системы врожденного иммунитета, способных к цитолизу инфицированных или трансформированных клеток без предварительной сенсибилизации. Естественные киллеры выявлены в различных органах и тканях и могут отличаться по фенотипическим и функциональным характеристикам в зависимости от локализации. Например, естественные киллеры являются преобладающей популяцией лимфоцитов децидуальной оболочки матки на ранних сроках беременности, их доля может составлять до 70%. В матке NK-клетки могут контактировать с клетками трофобласта плода, в отношении которых также могут проявлять цитотоксичность. Естественные киллеры регулируют инвазию клеток трофобласта в матку, способствуют ремоделированию спиральных артерий и установлению физиологичного кровотока между организмами матери и плода. Обсуждается вклад нарушения функциональной активности NK-клеток в патогенез ранних репродуктивных потерь и бесплодия, вызванного иммунными факторами. Для лечения бесплодия применяют различные препараты, среди которых иммуноглобулины для внутривенного введения (ВВИГ) и рекомбинантный гранулоцитарный колониестимулирующий фактор (G-CSF). Показано увеличение вероятности имплантации эмбриона и частоты успешных вынашиваний плода у женщин, получавших терапию этими препаратами. Предполагают, что эти препараты могут оказывать влияние на фенотип и функциональную активность NK-клеток. Актуально изучение эффектов препаратов ВВИГ и G-CSF на рецепторный профиль NK-клеток.

Адрес для переписки:

Давыдова Алина Алексеевна
ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта»
199034, Россия, Санкт-Петербург, Менделеевская линия, 3.
Тел.: 8 (812) 328-98-50.
E-mail: alyadavydova@gmail.com

Address for correspondence:

Alina A. Davydova
D. Ott Research Institute of Obstetrics, Gynecology and Reproductology
3 Mendeleevskaya Line
St. Petersburg
199034 Russian Federation
Phone: +7 (812) 328-98-50.
E-mail: alyadavydova@gmail.com

Образец цитирования:

А.А. Давыдова, В.А. Михайлова, А.А. Ковалева, П.В. Гребенкина, Е.В. Тыщук, М.С. Зементова, О.Н. Беспалова, Д.И. Соколов, С.А. Сельков «Препараты иммуноглобулинов для внутривенного введения и рекомбинантного гранулоцитарного колониестимулирующего фактора влияют на экспрессию цитотоксических рецепторов NK-клеток» // Медицинская иммунология, 2024. Т. 26, № 6. С. 1301-1308. doi: 10.15789/1563-0625-IIA-2872

For citation:

A.A. Davydova, V.A. Mikhailova, A.A. Kovaleva, P.V. Grebenkina, E.V. Tyshchuk, M.S. Zementova, O.N. Bespalova, D.I. Sokolov, S.A. Selkov "Intravenous immunoglobulins and recombinant granulocyte-colony stimulating factor modulate expression of NK cytotoxic receptors", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2024, Vol. 26, no. 6, pp. 1301-1308. doi: 10.15789/1563-0625-IIA-2872

DOI: 10.15789/1563-0625-IIA-2872

Целью настоящей работы была оценка экспрессии цитотоксических рецепторов клеток линии NK-92 в присутствии препаратов ВВИГ и рекомбинантного G-CSF.

В работе использовали клетки линии NK-92 в качестве эффекторов и клетки трофобласта линии JEG-3 в качестве клеток-мишеней. Клетки культивировали совместно в присутствии одного из препаратов, а также без добавления препаратов. С помощью проточной цитометрии оценивали экспрессию клетками NK-92 рецепторов CD45, CD56, CD215, KIR2DL3, KIR2DS4, NKG2D, NKp44, NKp30.

Установлено, что количество клеток линии NK-92, экспрессирующих рецепторы NKG2D, NKp30, KIR2DL3 и интенсивность экспрессии рецепторов NKG2D и NKp30, снижены в присутствии препаратов ВВИГ. В присутствии препарата G-CSF и клеток трофобласта снижено количество $KIR2DL3^+$ и $NKp44^+$ NK-клеток.

Полученные результаты могут быть связаны как с непосредственным, так и с косвенным влиянием исследуемых препаратов на фенотип NK-клеток.

Ключевые слова: NK-клетки, NK-92, трофобласт, JEG-3, иммуноглобулины для внутривенного введения, гранулоцитарный колониестимулирующий фактор, цитотоксические рецепторы

INTRAVENOUS IMMUNOGLOBULINS AND RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR MODULATE EXPRESSION OF NK CYTOTOXIC RECEPTORS

Davydova A.A., Mikhailova V.A., Kovaleva A.A., Grebenkina P.V., Tyshchuk E.V., Zementova M.S., Bespalova O.N., Sokolov D.I., Selkov S.A.

D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation

Abstract. Natural killer cells (NK cells) are a population of innate immune lymphocytes capable of cytolysis of infected or transformed cells without prior sensitization. Natural killers are detected in various organs and tissues and may differ in phenotypic and functional characteristics depending on localization. For example, NK cells are the dominant population (up to 70%) of decidual lymphocytes in early pregnancy. NK cells are able to contact with trophoblast cells, exert cytotoxicity towards them, as well as regulate their invasion, contributing to spiral arteries remodeling and establishment of physiological blood flow between mother and fetus. The contribution of impaired NK cell functional activity to immune mechanisms of the reproductive disorders is widely discussed. Various drugs are used to treat infertility, including intravenous immunoglobulins (IVIG) and recombinant granulocyte colony stimulating factor (G-CSF). Increased rates of embryo implantation and higher frequency of successful gestation have been shown after treatment with these drugs. The effect of these drugs on NK cells phenotype and functional activity is assumed, thus requiring further studies on the effects of IVIG and G-CSF on the receptor profile of NK cells.

The aim of this work was to evaluate expression of cytotoxic receptors on the NK-92 cells in presence of IVIG and recombinant G-CSF preparations.

NK-92 cells were used as effectors, and trophoblast-derived JEG-3 line served as target population. The cells were co-cultured in presence of drugs, as well as without them. Expression of CD45, CD56, CD215, KIR2DL3, KIR2DS4, NKG2D, NKp44, NKp30 receptors by NK-92 cells was evaluated by flow cytometry.

The number of NK-92 cells expressing NKG2D, NKp30, KIR2DL3 receptors and the expression intensity of NKG2D and NKp30 receptors were reduced in presence of IVIG preparations. The numbers of $KIR2DL3^+$ and $NKp44^+$ NK cells were reduced when supplied with G-CSF and trophoblast cells.

The obtained results may be associated with both direct and indirect effects of the studied drugs on the NK cell phenotype.

Keywords: NK cells, NK-92, trophoblast, JEG-3, intravenous immunoglobulins, granulocyte colony stimulating factor, cytotoxic receptors

This research was supported by the the Ministry of Science and Higher Education of the Russian Federation, Research Program No. 122041500061-8.

Introduction

Natural killers are lymphocytes of the innate immune system, which are characterized by the manifestation of cytotoxicity against virus-infected or malignant cells in the body. The cytotoxic function of NK cells is regulated by the balance of signals from activating and inhibiting receptors. In addition to the antiviral and antitumor immune response, NK cells play an important role in the development of pregnancy. By developing cytotoxic activity against trophoblast cells invading the uterine wall and by secreting various cytokines, NK cells regulate trophoblast invasion, contributing to the establishment of the physiological blood flow between mother and fetus [13]. Violation of these processes can cause reproductive pathologies. For example, for women with recurrent miscarriage (RM), the increased cytotoxicity of peripheral blood NK cells against trophoblast cells of the JEG-3 line was shown *in vitro*, in comparison with healthy non-pregnant women [13]. Data on the cytotoxicity of NK cells at infertility and sterility state are contradictory. A number of studies have shown the increased cytotoxicity of peripheral blood NK cells in women with RM and implantation failures, comparing to healthy women [9]. At the same time, a meta-analysis of Seshadri S. & Sunkara S.K. (2014) evaluating the role of NK cells in the outcomes of *in vitro* fertilization (IVF) revealed no differences in live birth rates in women with increased cytotoxicity of NK cells compared to women with NK cell cytotoxicity lying withing the normal range.

For treatment of infertility associated with immune factors, IVIG and recombinant G-CSF treatment are used. It has been shown that the use of IVIG in preparation for IVF procedure increases the probability of successful embryo implantation [6]. Previously, we have established the cytoprotective effect of IVIG against trophoblast cells during their contact interaction with NK cells in an *in vitro* model [7], however, the mechanism of IVIG effects is not clearly defined at the moment.

Data on the use of recombinant G-CSF are also ambiguous. In one of the studies, the frequency of successful termination of pregnancy in women with RM receiving G-CSF therapy was almost twice as high as in women with RM receiving placebo [10]. At the same time, the positive effect of G-CSF on pregnancy development in women with a history of three or more unsuccessful IVF attempts has not been confirmed [1].

Thus, IVIG and G-CSF are used in clinical practice to increase the likelihood of developing a successful pregnancy. However, the data on the direct effect of these drugs on NK cells are contradictory that requires additional research. In this regard, **the aim of the work** was to evaluate the expression of cytotoxic receptors of NK-92 line cells in the presence of IVIG preparations and recombinant G-CSF.

Materials and methods

We used NK-92 line cells (ATCC, USA) with phenotypic and functional characteristics of activated NK cells, as well as cells of the JEG-3 line cells (ATCC, USA), corresponding in their characteristics to the extracellular trophoblasts of the first trimester of pregnancy. The cells were cultured according to ATCC protocols.

The expression of cytotoxic receptors by NK-92 line cells was assessed after culturing cells with G-CSF at a concentration of 400,000 IU per 100 μL of medium and with IVIG at concentrations of 12 mg/mL and 6 mg/mL. In addition, the expression of receptors by NK-92 line cells was evaluated in case of incubation with trophoblast cells of the JEG-3 line, in the presence of G-CSF or IVIG at the above mentioned concentrations.

Recombinant IL-2 (Biotech, Russia) was added to the NK-92 line cells at a concentration of 500 IU/mL. Cells were placed in the wells of a round-bottomed 96-well plate at concentration of 150,000 cells per 100 μL of medium. A recombinant G-CSF at a concentration of 400,000 IU/100 μL was added to the part of the wells. The cells were incubated for 24 hours at 37 °C and 5% CO_2. The next day, trophoblast cells of the JEG-3 line were added to NK-92 line cells at concentration of 30,000 cells per 50 μL of medium. In part of the wells with NK-92 line cells without the G-CSF preparation, the drug IVIG was added at concentrations 12 mg/mL and 6 mg/mL. The cells were settled by centrifugation at 100g for 3 minutes. Then the cells were incubated for 4 hours at 37 °C and 5% CO_2. After incubation, the cells were treated with a Hanks solution containing 1% embryonic calf serum, the samples were incubated for 10 minutes at 4 °C. Then the cells were treated with antibodies to the receptors: CD45; CD56; CD215; KIR2DL3; KIR2DS4; NKG2D; NKp44; NKp30 (BD, USA). Isotypic antibodies were added to the part of the wells to control the nonspecific binding of the antibodies (BD, USA). The antibody-treated samples were incubated for 20 minutes in the dark at

room temperature. The samples were then analysed using a FACSCanto II flow cytofluorimeter, assessing the relative number of cells expressing receptors and the intensity of receptor expression on the surface of NK cells.

Statistical data processing was carried out using the GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Nonparametric Mann-Whitney test, Kraskel-Wallis test and Wilcoxon test were used.

Results and discussion

Analysis of NK-92 line cells expression of NKG2D activating receptor showed that the number of cells expressing it and the intensity of expression of this receptor were reduced in the presence of IVIG at concentrations of 12 mg/mL and 6 mg/mL (Figure 1A, B). Receptor NKG2D is an activating transmembrane protein of the CD94/NKG2 family of type C lectin receptors. NKG2D ligands are stress-induced proteins of the MIC and RAET1/ULBP families, which are expressed on the surface of malignant cells and infected cells. In the literature, there are few publications on the expression of NKG2D receptor in reproductive pathologies. In one of the studies, the level of NKG2D expression by peripheral blood NK cells in women with repeated implantation failures and in fertile non-pregnant women did not differ [15]. The decrease in the level of activating NKG2D receptor in the presence of IVIG, which we have established, is consistent with the decrease in the cytotoxic function of NK-92 line cells in the presence of IVIG shown earlier [7].

It was found that the addition of IVIG at concentrations of 12 mg/mL and 6 mg/mL to NK-92 line cells caused a decrease in the number of $NKp30^+$ NK cells, as well as a decrease in the intensity of their expression of NKp30 (Figure 1C, D). NK cell receptor NKp30 belongs to the family of natural cytotoxicity receptors. Its ligands BAG6 and B7-H6 are characteristic for virus-infected and tumour cells. Earlier, an *in vitro* model of interaction between dendritic cells and peripheral blood NK cells showed a decrease in the expression of NKp30 receptor by NK cells in the presence of IVIG [14]. However, in our work, the addition of trophoblast cells of the JEG-3 line did not cause significant changes in the expression of NKp30 receptor. There is also evidence of changes in NKp30 isoforms in peripheral blood and placenta at early pregnancy loss. The differences in receptor isoforms are also shown in women with elective termination of pregnancy compared to women with spontaneous miscarriage [12], but not in the overall level of NKp30 expression. Thus, the obtained data complement the literature data on the effect of drugs for RM and infertility treatment.

After incubation of NK cells with IVIG at the concentration of 6 mg/mL, the relative number of cells expressing the inhibitory receptor KIR2DL3 was increased compared to $KIR2DL3^+$ cells of the NK-92 line after cocultivation with JEG-3 line cells and IVIG line (Figure 1E). There were no changes in the intensity of KIR2DL3 expression (Figure 1F). Receptor KIR2DL3 belongs to the group of inhibitory receptors of the KIR group – transmembrane glycoproteins expressed by NK cells and T lymphocytes. The ligands for them are HLA class I molecules, which non-classical variants are present on trophoblast cells. The obtained results partially correspond to a decrease in the cytotoxic function of NK-92 line cells in presence of IVIG, which we showed earlier [7]. It should be noted that a whole spectrum of receptors is involved in NK cell realization of their cytotoxic potential. Therefore, IVIG possibly have not only a direct effect on NK cells, but also indirectly influence trophoblast cells. For example, it is shown that IVIG affect the expression of glycoprotein OX-2 of the immunoglobulin superfamily (CD200), which is expressed on trophoblast cells, as well as on endothelial and decidual cells, T and B lymphocytes, [3]. Its interaction with CD200R receptor leads to the synthesis of indolamine-2,3-dioxygenase by myeloid cells, as a result of which the proliferation of T lymphocytes and NK cells is inhibited and T regulatory lymphocytes are activated [4]. It is also possible that IVIG screen negatively charged membrane phospholipids of target cells (like "umbrella cover") [8]. Further studies are required to study the effect of the IVIG on the interactions of NK cells with trophoblast cells.

We found that the relative number of NK-92 line cells expressing KIR2DL3 inhibitory receptor after incubation with JEG-3 line trophoblast cells and G-CSF was reduced compared to the relative number of $KIR2DL3^+$ NK cells with G-CSF, but without trophoblast cells (Figure 2A). At the same time, there were no differences in the expression of KIR2DL3 between intact NK-92 line cells and NK-92 line cells with the addition of G-CSF. The intensity of KIR2DL3 expression in the presence of G-CSF also did not change (Figure 2B). According to the literature, trophoblast cells express a receptor for G-CSF [5]. *In vivo*, G-CSF is secreted by decidual macrophages and stimulates migration and invasion of trophoblast cells. The obtained data can be explained by the fact that in the presence of G-CSF, trophoblast cells acquire an invasive phenotype, which indirectly can cause changes in the phenotype of NK cells,

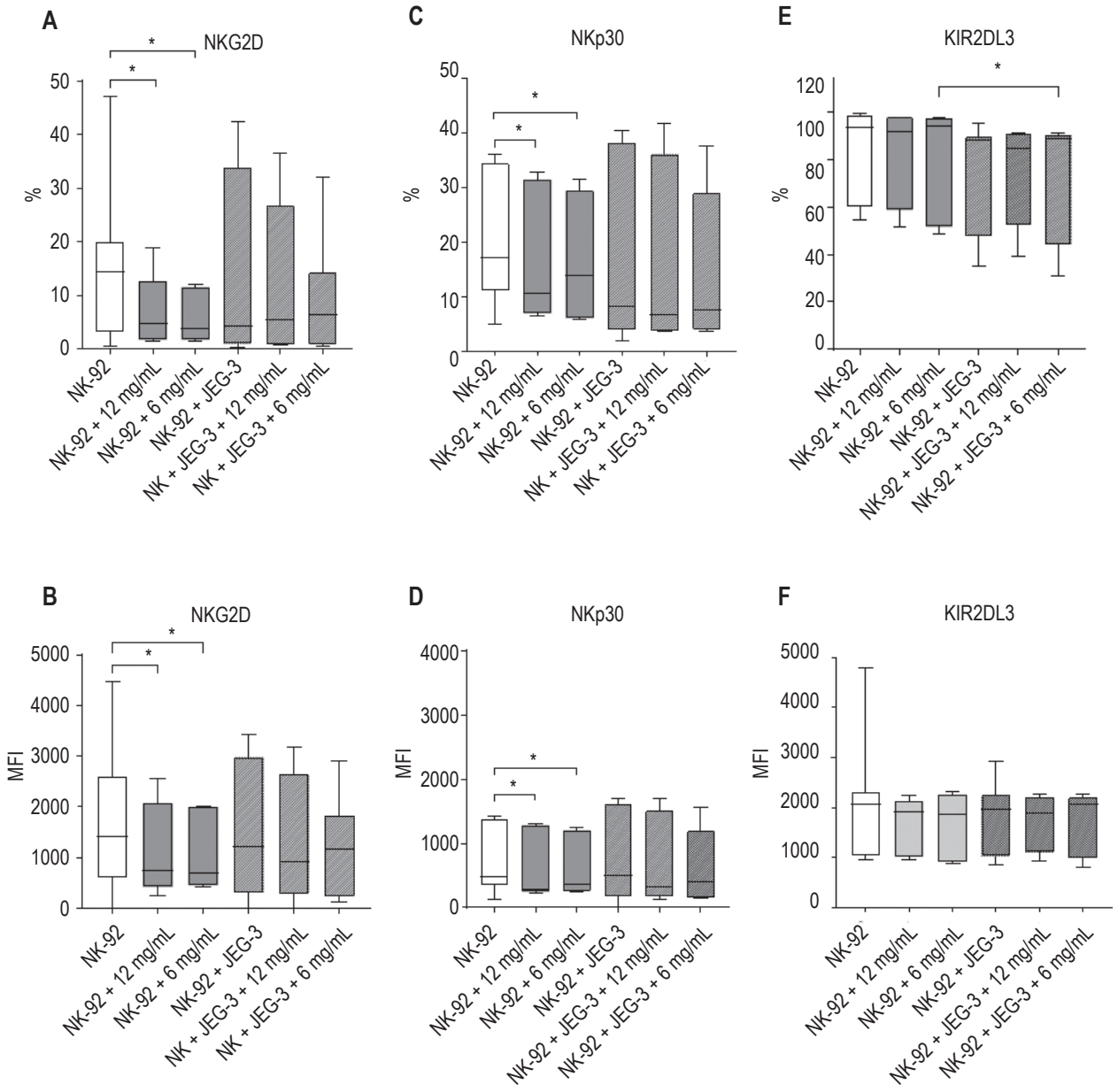

Figure 1. Relative number of NK-92 line cells expressing receptors (A) NKG2D, (C) NKp30, (E) KIR2DL3, as well as the intensity of expression (MFI) of these receptors (B, D, F) in presence of IVIG

Note. The significance of differences: *, $p < 0.05$.

leading to a decrease in the number of NK cells expressing inhibitory receptors, including KIR2DL3.

In this work, it was shown that the relative number of NK cells expressing NKp44 activating receptor after incubation with G-CSF was increased compared to the number of NKp44$^+$ NK-92 line cells in the presence of JEG-3 line cells and G-CSF (Figure 2C). There were no changes in the intensity of expression of this receptor in presence of G-CSF (Figure 2D). NKp44 receptor expression is specific to activated NK cells. Previously, a decrease in the relative number of NKp44$^+$ peripheral blood NK cells was shown after stimulation with IL-2 and IL-15 cytokines in the presence of G-CSF, compared with NK cells stimulated by IL-2 and IL-15 and without the addition of G-CSF [11]. The decrease in the number of NK cells expressing NKp44 may be due to both the direct effect of G-CSF on NK cells and an indirect effect

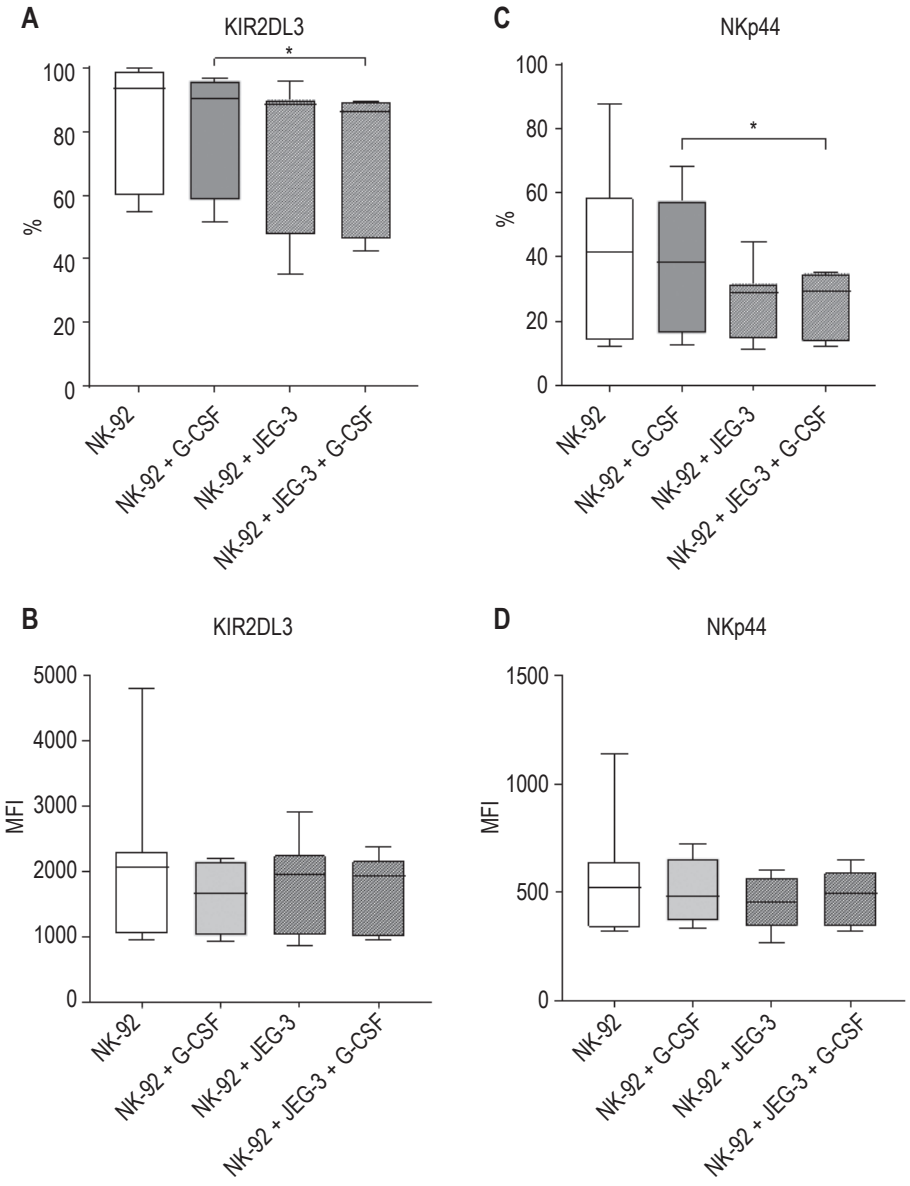

Figure 2. Relative number of NK-92 line cells expressing (A) KIR2DL3 and (C) NKp44, as well as the intensity of expression (MFI) of these receptors (B, D) in presence of recombinant G-CSF

Note. The significance of differences: *, $p < 0.05$.

involving trophoblast cells. There were no differences in the expression of other NK cell receptors in the presence of IVIG and G-CSF preparations.

Conclusion

Thus, the effect of the IVIG on the expression of NKG2D and NKp30 receptors by NK cells in a model using NK-92 line cells was established. It has been demonstrated that in the presence of trophoblast cells of the JEG-3 line, IVIG and G-CSF contribute to a decrease in the number of NK cells expressing the KIR2DL3 receptor. G-CSF caused a decrease of the number of NK cells expressing NKp44 in the presence of trophoblast cells. The results obtained can be associated with both direct and indirect effects of the studied drugs on the phenotype of NK cells.

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Авторы:

Давыдова А.А. *– младший научный сотрудник лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Михайлова В.А. *– к.б.н., старший научный сотрудник лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Authors:

Davydova A.A., *Junior Research Associate, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Mikhailova V.A., *PhD (Biology), Senior Research Associate, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Ковалева А.А. *– лаборант лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Гребенкина П.В. *– младший научный сотрудник лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Тыщук Е.В. *– младший научный сотрудник лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Зементова М.С. *– лаборант лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Беспалова О.Н. *– д.м.н., заместитель директора по научной работе ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Соколов Д.И. *– д.б.н., заведующий лабораторией межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Селькov С.А. *– профессор, заслуженный деятель науки РФ, руководитель отдела иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Kovaleva A.A., *Laboratory Technician, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Grebenkina P.V., *Junior Research Associate, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Tyshchuk E.V., *Junior Research Associate, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Zementova M.S., *Laboratory Technician, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Bespalova O.N., *PhD, MD (Medicine), Deputy Director, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Sokolov D.I., *PhD, MD (Biology), Head, Laboratory of Intercellular Interactions, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Selkov S.A., *Professor, Honored Scientist of the Russian Federation, Head, Department of Immunology and Intercellular Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Pertersburg, Russian Federation*

Поступила 17.05.2023
Отправлена на доработку 04.07.2023
Принята к печати 04.10.2023

Received 17.05.2023
Revision received 04.07.2023
Accepted 04.10.2023