ОСОБЕННОСТИ ДИФФЕРЕНЦИРОВКИ NK-КЛЕТОК: CD56^{dim} И CD56^{bright} NK-КЛЕТКИ ВО ВРЕМЯ И ВНЕ БЕРЕМЕННОСТИ

Михайлова В.А.[1, 2], Белякова К.Л.[1], Сельков С.А.[1], Соколов Д.И.[1, 2, 3]

[1] ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия
[2] ГБОУ ВПО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[3] ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия

Резюме. NK-клетки представляют собой лимфоциты, способные к контактному цитолизу вирус-инфицированных клеток и опухолевых клеток и являющиеся источником цитокинов, стимулирующих другие клетки иммунной системы и способствующих развитию иммунного ответа. Дифференцировка NK-клеток связана с последовательным приобретением стволовыми клетками специфичных для NK-клеток рецепторов и становлением функциональных характеристик натуральных киллеров. Целью настоящего обзора было рассмотрение CD56^{dim} и CD56^{bright} популяций NK-клеток в процессе их дифференцировки. В обзоре описаны поверхностные рецепторы NK-клеток и экспрессия ими транскрипционных факторов на разных стадиях дифференцировки, представлена сравнительная характеристика данных о влиянии цитокинов и клеток микроокружения на процесс дифференцировки NK-клеток, рассмотрено явление существования NK-клеток, подобных клеткам памяти. Особый интерес представляет дифференцировка NK-клеток матки, так как эти клетки являются особой популяцией NK-клеток, которая преобладает среди лимфоцитов децидуальной оболочки при беременности и принимает участие в процессе образования и ремоделирования плаценты. В обзоре рассмотрены особенности дифференцировки NK-клеток матки, учитывая возможность образования этой популяции NK-клеток как из NK-клеток периферической крови, так и пролиферации *in situ*. Изучение особенностей функционального состояния NK-клеток матки позволит в дальнейшем приблизиться к пониманию роли NK-клеток при беременности и нарушению оказываемой NK-клетками регуляции в зоне маточно-плацентарного контакта при патологии беременности.

Ключевые слова: NK-клетки, дифференцировка, беременность, поверхностные рецепторы, цитокины, NK-клетки матки, децидуальные NK-клетки

PECULIARITIES OF NK CELLS DIFFERENTIATION: CD56^{dim} AND CD56^{bright} NK CELLS AT PREGNANCY AND IN NON-PREGNANT STATE

Mikhailova V.A.[a, b], Belyakova K.L.[a], Selkov S.A.[a], Sokolov D.I.[a, b, c]

[a] D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg, Russian Federation
[b] The First St. Petersburg I. Pavlov State Medical University, St. Petersburg, Russian Federation
[c] Institute of Experimental Medicine, St. Petersburg, Russian Federation

Abstract. Natural killer (NK) cells represent a lymphocyte subpopulation which is capable of contact cytolysis of virus-infected cells and tumor cells, being a source of cytokines which stimulate other immune

Адрес для переписки:
Соколов Дмитрий Игоревич
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: falcojugger@yandex.ru

Address for correspondence:
Sokolov Dmitry I.
D. Ott Research Institute of Obstetrics, Gynecology and Reproductology
199034, Russian Federation, St. Petersburg, Mendeleevskaya Line, 3.
Phone: 7 (812) 328-98-50.
E-mail: falcojugger@yandex.ru

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cells and promote immune response. NK cell differentiation is connected with a consequent acquisition of specific NK cell receptors by stem cells and formation of functional characteristics inherent to natural killer cells. The aim of this review was to describe the $CD56^{dim}$ and $CD56^{bright}$ populations of NK cells in the course of their differentiation. The authors describe NK surface receptors and expression of transcription factors at various steps of the NK differentiation. We present comparative characteristics of data concerning cytokines and cellular microenvironment influence upon NK cell differentiation, and examine a phenomenon of existing memory-like NK cells. Uterine NK cell differentiation is of special interest, since these cells represent a special NK cell population which prevails among decidual lymphocytes during pregnancy and participates in the process of placental formation and development. This review considers some features of uterine NK cell differentiation, taking into account a possibility of formation of this NK cell population from both peripheral blood NK pool, and *in situ* proliferation. Moreover, functional studies of the uterine NK cells allow to get closer to understanding the role of NK cells during pregnancy and abnormality of utero-placental bed regulation by NK cells in cases of pregnancy failure.

Keywords: NK cells, differentiation, pregnancy, cell surface receptors, cytokines, uterine NK cells, decidual NK cells

Introduction

Natural killer (NK) are a part of innate immunity system and represent lymphocytes, which are capable of contact cytolysis of virus infected cells and tumor cells and are the source of cytokines stimulating other cells of the immune system and promoting immune response development [3]. NK cells in humans are present naturally in most organs and tissues, including bone marrow, thymus, lymph nodes, blood, skin, intestines, liver, lungs, uterus [6, 37]. NK cells are often addressed as $CD3^-CD56^+$ lymphocytes although the expression pattern of NK cells includes variety of receptors including killer immunoglobulin-like receptors (KIR) [38], CD16 (Fcγ-receptor III), which mediates antibody-dependent cellular cytotoxity [25, 32], natural killer group (NKG) receptors, cytotoxic receptors NKp30, NKp44, NKp46 [20]. NK cells differentiation and development is connected with the consequent change of repertoire of receptors present in the cell and their acquisition of functional properties. Studying different aspects of NK cell differentiation in humans especially during pregnancy is of special interest, because NK cells functional and phenotypic specifics are closely connected with healthy pregnancy.

1. Development of NK cells main populations

1.1. NK cells populations' development in fetus

Mainly NK cells are present in tissues as intraepithelial lymphocytes, however, NK cells can also form cell clusters, such as in Peyer's glands and mesenterial lymph nodes [6]. In peripheral blood, mature NK cells are characterized by broad spectrum expression of KIR, having both activation and inhibitory activity [2]. NK cell differentiation and their expression of KIR begin at early stages of fetus development [14]. Mainly, NK cells locate in such fetus organs as liver and lungs, also NK cells are present in fetal spleen. Less NK cells are found in bone marrow and mesenterial lymph nodes [14]. Fetus NK cells are characterized by phenotype $CD7^+CD161^+CD3^-CD14^-CD19^-CD45^+$, and also by high expression of CD56 [19], as the result of which it seems to be impossible to divide fetus NK cell populations into $CD56^{dim}$ and $CD56^{bright}$ cells[1] as in adults [14]. NK cell differentiation in fetus is evaluated by level of NKG2A and CD16 receptors expression. It has been demonstrated that the ratio of NK cell populations $NKG2A^+CD16^-$ (that can be corresponded to $CD56^{bright}$ population in adults), $NKG2A^+CD16^+$ and $NKG2A^-$ $CD16^+$ (that can be corresponded to $CD56^{dim}$ population in adults) does not change at the gestational age from 15 weeks to 22 weeks, which indicates that NK cell differentiation takes place before the 15^{th} week of pregnancy [14]. The character of KIR receptor expression by fetus NK cells varies depending on cell localization: the highest expression of KIR is found in NK cells, localized in fetus lungs. Like in adult organisms, an expression of large repertoire of KIR is connected with NK cell differentiation: the highest density of KIR is typical for NK cell populations $NKG2A^+CD16^+$ and $NKG2A^-$ $CD16^+$. The expression of CD57, which is a marker of terminal stages of NK cell differentiation, is set for $NKG2A^-CD16^+$ [14], which indicates higher maturity level of these cells.

Comparing fetal NK cells and peripheral blood NK cells in an adult person, it was stated that NK cells of both groups can induce death of cells, which were not expressing MHC-1 locus molecules. However, compared to adult NK cells, fetal NK cells are characterized by lower cytotoxic activity [14, 19], but higher ability to respond to cytokine stimulation (IL-12, IL-18) [14]. Fetal NK cells localized in lungs contain perforin and granzyme B, while perforin and granzyme B content increases as NK cells differentiate from $NKG2A^+CD16^-$ in $NKG2A^-CD16^+$, which indicates maturation of functional apparatus of fetal NK cells during differentiation [14].

[1] dim – low expression of receptor; bright – high expression of receptor

1.2. NK cells populations' development in adults

1.2.1. Characteristics of two main populations of NK cells ($CD56^{bright}$ and $CD56^{dim}$)

In adult organisms, the main source of hematopoietic stem cells, which can differentiate in NK cells, is bone marrow [2, 20]. NK cells can circulate [6] and continue their differentiation in spleen, tonsils and lymph nodes [20]. In secondary lymphoid tissue, NK cell progenitors pass differentiation to the stage of immature NK cells [20], which, in turn, develop into NK cells with phenotype $CD56^{dim}CD16^{bright}$, prevailing in blood flow, and $CD56^{bright}CD16^{dim}$ NK cells, placed in liver, endometrium, decidua and lymph nodes [3]. Recently $CD56^{bright}CD16^{dim}$ NK cells are viewed as precursors of $CD56^{dim}CD16^{bright}$ NK cells [37]. While differentiation NK cells acquire functional receptors, connected with their cytotoxic function. In the beginning an expression of CD94/NKG2A, NKp46, NKG2D receptors is observed, and then an expression of KIR and CD16 receptors [37].

$CD56^{dim}CD16^{bright}$ NK cells, present in peripheral blood and spleen, are characterized by increased cytotoxic activity and expression of broad spectrum of KIR, as well as cytotoxic receptors NKp30, NKp44, NKp46 [20]. While culturing of $CD56^{dim}CD16^{bright}$ NK cells with K562 cells, an increase of IFNγ, TNFα, MIP-1α, MIP-1β production by NK cells was demonstrated [9].

The $CD56^{bright}CD16^{dim}$ population of NK cells is mainly present in lymph nodes and tonsils, and in blood, it makes up less than 10% of NK cell population [20]. For $CD56^{bright}CD16^{dim}$ NK cells, reduced cytotoxic activity and reduced expression of NKp46 receptors is typical [20]. In presence of K562 the $CD56^{bright}CD16^{dim}$ population of NK cells does not significantly change cytokine production, however, with combined stimulation by IL-12 and IL-18 cytokines, it demonstrates an increased production of IFNγ compared to $CD56^{dim}CD16^{bright}$NK cells [9]. Often the $CD56^{bright}CD16^{dim}$ population of NK cells is combined with $CD56^{bright}CD16^{-}$NK cells, indicating the general population $CD56^{bright}CD16^{-/dim}$, and noting that the defining marker of these populations is CD56, while CD16 does not mediate the main functional properties of these cells [6, 20, 35]. As the result of activation both *in vivo* (after etering lymph node with afferent lymph) and *in vitro* NK cells with $CD56^{bright}$ $CD16^{dim}$ phenotype can acquire an increased content of perforin and a phenotype of $CD56^{dim}CD16^{bright}$NK cells: KIR^{+} IL-7R^{-} c-kit ($CD117^{-}$) $CXCR3^{-}CCR7^{-}$ $CD62L^{-}$ [6]. Table 1 shows information about the surface receptor expression by NK-cells at different stages of differentiation.

1.2.2. Transcription factors in NK cells development process

Differentiation of NK cell is characterized by expression of a certain set of transcription factors. Using the analysis of expressed mRNA in the *in vitro* model of human NK cells differentiation obtained from umbilical vein, it was determined that at the stage of transfer from stem cells to NK cell progenitors, E4BP4 and TOX transcription factors participate [28]. While differentiation of NK cell progenitors into mature NK cells an expression of the transcription factors Ikaros, EGF1 and PU.1 is observed [28]. There is a high expression of transcription factors EGR-2, ID-2, and T-bet at all stages of NK cell differentiation. An expression of Gata-3 transcription factor in NK cell progenitors decreases for the short time and then restores to the initial level. High expression of EGR-2, ID-2, T-bet, and Gata-3 factors is connected with their participation in all stages of NK cell differentiation and in acquisition of functional properties by NK cells [28]. Transcription factor IRF-2, apparently, participates in maintenance of differentiated NK cell pool, because a defect of this protein results in an increase of intensity of NK cell apoptosis [28]. It was also demonstrated *in vitro* that, as the result of IL-12 impact on mature NK cells, an expression of transcription factor ID3 mRNA

TABLE 1. SURFACE RECEPTORS OF HUMAN NK-CELLS DEFINING THE STAGES OF THEIR DIFFERENTIATION

Differentiation stage	Localization	Surface receptors
Hematopoietic stem cell	Bone marrow [2, 20]	$CD34^{+}CD38^{dim}CD45RA^{-}CD10^{-}$ [37]
Stage 1	Bone marrow [2, 20]	$CD34^{+}CD117^{-}CD94^{-}CD16^{-}CD45RA^{+}CD10^{+}$ [20, 37]
Stage 2	Secondary lymphoid tissue [20]	$CD34^{+}CD117^{+}CD94^{-}CD16^{-}CD45RA^{+}CD10^{-}$ $CD161^{+}Integrin\beta7^{bright}$ [10, 20, 37]
Stage 3	Secondary lymphoid tissue [20]	$CD34^{-}CD117^{+}CD94^{-}CD16^{-}CD11a^{+}CD161^{+}NKp44^{-}CD56^{-}$ [13,10, 37]
Stage 4 $CD56^{bright}$	Liver, uterine endometrium, decidua, lymph nodes [3, 20]	$CD34^{-}CD117^{+/-}CD94^{bright}CD16^{-/dim}$ $CD11a^{+}CD56^{bright}NKp46^{dim}$ [3, 20, 37]
Stage 5 $CD56^{dim}$	Peripheral blood, spleen [3, 20]	$CD34^{-}CD117^{-}CD94^{+/-}CD16^{+/bright}KIR^{+/-}$ $CD56^{dim}NKp30^{+}NKp44^{+}NKp46^{+}CXCR3^{-}CCR7^{-}CD62L^{-}$ [3, 6, 20, 37]
Stage 6 (Memory cell)	Peripheral blood [30]	$NKG2A^{+}CD94^{+}NKp46^{+}CD69^{+}$ [30]

increases, while an expression of Gata3 and TOX reduces [18].

1.2.3. Non-linear character of NK cells populations` development

Despite the attempts to determine a sequence of NK cell developmental stages, current data on nonlinear character of NK cell differentiation appear in literature, in particular, depending on their localization and microenvironment. In the experiments on mice, transformed by human plasmids of cytokines IL-15 and Flt-3L, it was demonstrated that from common progenitor of myeloid cells, for which $CD56^-CD36^-CD33^+CD34^+NKG2D^-NKp46^-$ phenotype is typical, myeloid progenitors of NK cells with $CD56^{dim}CD36^+CD33^+CD34^-NKG2D^-NKp46^-$ phenotype are differentiated. Then, these progenitors of NK cells acquire a phenotype of $CD56^{bright}CD36^-CD33^-CD34^-NKG2D^+NKp46^+$NK cells [7]. The investigation also determined presence of myeloid progenitors of NK cells in humans in umbilical vein blood, as well as in fetal bone marrow and in bone marrow of an adult human [7]. Furthermore, it described presence of special populations of NK cell progenitors with $DX5^-CD49a^+$ phenotype, which were formed in the liver from $CD45.1^+NK1.1^-CD3^-CD19^-$NK cells of the spleen and were not detected in bone marrow [26].

1.2.4. Phenomenon of "memory-like NK cells"

Currently, a possibility of existence of memory-like NK cells, which may be formed both by $CD56^{bright}$ and $CD56^{dim}$ NK cells [30] and be a final stage of NK cell differentiation, is discussed in literature [37]. The term memory-like NK cells, which means NK cells similar to memory cells, is used in literature. Some scientists point out three possible variants of memory-like NK cells, which differ by mechanism of formation and functional characteristics: virus dependent induction, cytokine induction, and existence of specialized population of memory-like NK cells in liver [24]. A capacity of NK cells, previously activated by IL-12 and IL-18 cytokines, after a certain period of time (from 7 to 21 days) at repeated cytokine stimulation to produce an increased number of IFNγ compared to control was described [30]. At the same time, NK cell cytotoxicity evaluated by CD107a does not differ between the so-called memory NK cells and intact NK cells [30]. As NK cells have no antigen-induced differentiation, the term "memory NK cells" seems to be incorrect. Based on hypothetical mechanisms of memory-like NK cell induction, the most correct term seems to be "pre-activated NK cells". Currently, no markers unique to pre-activated NK cells were detected, however, a correlation between capacity to produce IFNγ by pre-activated $CD56^{bright}$ NK cells and expression of NKG2A/CD94 receptor is determined, as well as correlation between capacity to produce IFNγ by pre-activated NK cells of both populations ($CD56^{bright}$ and $CD56^{dim}$) and expression of NKp46 receptor [30]. It should be noted that the population of pre-activated $CD56^{bright}$ NK cells secrete more IFNγ than $CD56^{dim}$ NK cells after repeated stimulation both by cytokines and cells of leukemia cell line K562 [30]. These factors indicate alteration of functional properties of NK cells as the result of preliminary activation by cytokines and preservation of these alterations during a few days. There are evidences of pre-activation of NK cells not only *in vitro*, but also *in vivo*: in humans an adaptive change of NK cells properties induced by cytomegalovirus (CMV) infection occurs, it implies change in cytokine secretion and activating receptor NKG2C expression [29]. The mechanisms determining a phenomenon of pre-activation for NK cells are poorly known. Currently it is shown that pre-activated NK cells do not differ from intact NK cells by their content of phosphorylated forms of proteins STAT4 and STAT3, as well as by their content of IFNγ mRNA, which indicates the presence of post-transcriptional and post-translational mechanisms of memory induction at NK cells [30].

Thus, NK cell differentiation process in humans is connected with activation of transcriptional factors E4BP4, TOX, Ikaros, EGF1, PU.1, EGR-2, ID-2, IRF-2, T-bet, Gata-3 [28], and consequential change of repertoire of cell surface receptors, particularly acquirement of receptors CD56, CD94/NKG2A, NKp46, NKG2D, NKp30, NKp44, receptors KIR, CD16 [14, 20, 28]. Currently, two main populations of human NK cells are distinguished: $CD56^{dim}CD16^{bright}$ and $CD56^{bright}CD16^{dim}$ [3]. They are also supposed to represent two consequent stages of NK cell differentiation and their possible transfer from $CD56^{bright}CD16^{dim}$ to $CD56^{dim}CD16^{bright}$ cells [37]. Generally, the role of NK cells is realized in elimination virus-infected and tumor cells from organism, however, at such physiological state as pregnancy NK cells actively participate in the process of blastocyst implantation and placenta development. Despite investigations conducted of NK cell participation in pregnancy development, peculiarities of NK cell differentiation in placenta are poorly described.

2. Phenotype and functions of uterine NK cells at pregnancy

2.1. Presence of NK cells in uterus

NK cells make up a special population of uterine cells that significantly changes their representation in uterus depending on menstrual cycle phase and pregnancy. According to some data, decidual NK cells and endometrium NK cells differ little by phenotypic characteristics [22]. For endometrium NK cells an expression of activation receptors NKp46 and NKG2D

and lack or low expression of CD16, NKp44, NKp30 is typical while for decidual NK cells an expression of NKp46, NKG2D, NKp30, NKp44 is typical [23]. At pregnancy an IL-15 secretion by placenta is set [4], in presence of which activation of endometrial NK cells, their secretion of IFNγ and IP-10, higher expression of NKp46, NKp30, NKp44, NKG2D take place [23]. Thus, endometrial NK cells at pregnancy can change their phenotype and start a population of decidual cells. Then, during the first trimester, an increase of uterine NK cell numbers takes place, which make up from 50% to 90% of lymphoid cells, present in uterus [11]. Such alteration of NK cell number in the zone of uteroplacental bed may be due to migration of NK cells from peripheral blood [2, 27] through expressing receptors to chemokines produced by cells of decidua [1].

2.2. Peculiarities of uterine NK cell differentiation at pregnancy

According to literature data, the final stages of NK cell differentiation represent transfer from $CD56^{bright}$ to $CD56^{dim}$ phenotype [37]. Apparently, this process has a reversible nature, as decidua NK cells differ from $CD56^{bright}$ NK cells of peripheral blood by expression of inhibiting receptors, for which $CD56^{bright}$ $CD16^{dim/-}$ phenotype, CD94 expression, and high content of cytolytic granules are typical [6, 20]. Also as opposed to NK cells of peripheral blood decidual NK cells to a far greater extent can bind HLA-G, expressed at trophoblast cells [34]. Probably, as the result of influence of cytokines, secreted in the zone of uteroplacental bed, alteration of $CD56^{dim}$ phenotype of NK cells of peripheral blood and their acquisition of $CD56^{bright}$ phenotype of decidual NK cells [2]. Such alteration of NK cell phenotype in placenta at pregnancy is a continuation of NK cell differentiation *in situ*.

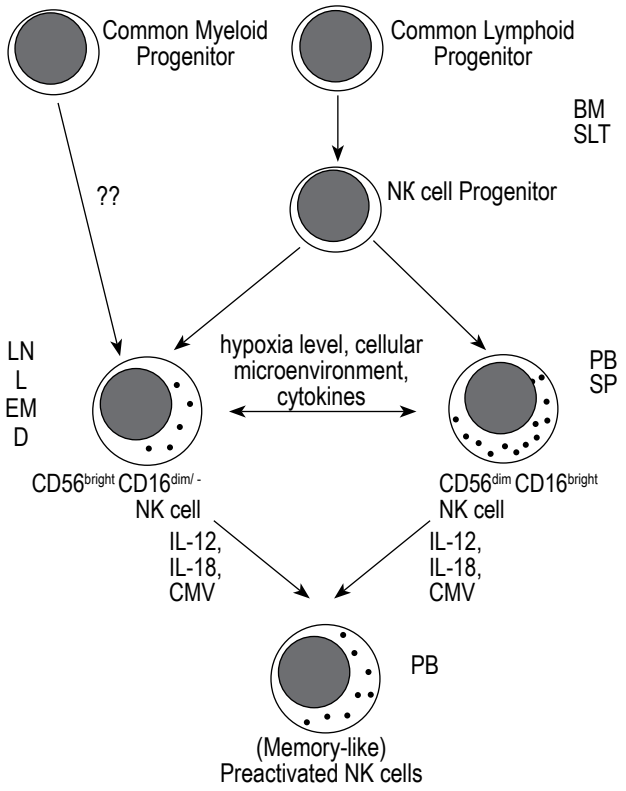
2.2.1. Oxygen supply modifiers NK cells differentiation at pregnancy

Significant influence on differentiation of NK cells of peripheral blood into decidua NK cells is exerted by modifying oxygen supply to tissue. At early gestational age after blastocyst invasion, but before rearrangement of spiral arteries, the cells, present in fetal-placental complex, are in hypoxic conditions [15]. During the first trimester, the oxygen partial pressure in fetal-placental complex makes up about 20 mm of mercury (2%) and increases to about 60 mm of mercury (10%) through the 12^{th} week of pregnancy. In decidua oxygen, partial pressure at the beginning of pregnancy constitutes 50 mm of mercury (8%) and in the end of the first trimester it increases up to 70 mm of mercury (12%), in proximity of spiral arteries it reaches 90-100 mm of mercury (20%) [36]. In the experiments with NK cells obtained *in vitro* from human hematopoietic stem cells, it was detected that in hypoxic conditions (1% O_2) NK cells decrease expression of NKp30 and NKG2D activation markers [38]. At 10% O_2 decidual NK cells restore expression of NKG2D receptor, and at 21% O_2 decidual NK cells reduce CD56 expression compared to culturing conditions at 10% O_2 [36]. At combined culturing of trophoblast cells line (SGHPL-4) and decidual NK cells with 10% O_2, the higher invasive activity of trophoblast and higher trophoblast capacity to form capillary-like structures is determined [36], which reflects the situation *in vivo*, when in the end of first trimester trophoblast invasion into uterus spiral arteries and establishment of uteroplacental blood supply takes place [16]. Thus, decidual cells, being in dynamic hypoxic conditions in placenta, can change their phenotype, reducing expression of receptors mediating cytotoxicity, and provide for regulation of uteroplacental bed development.

2.2.2. Cellular and cytokine microenvironment influences NK cells differentiation at pregnancy

Differentiation of NK cells of peripheral blood into decidua NK cells is influenced by cellular and cytokine microenvironment. Thus, combined culturing of NK cells of peripheral blood with decidual stromal cells results in reduction of NKp44, NKp30, NKG2D, DNAM-1 expression by NK cells of peripheral blood [8] and approaching of NK cell phenotype to the phenotype typical for decidual NK cells. Furthermore, binding of chemokine CXCL12 (SDF-1), secreted by placenta cells, leads to reduction of expression of NKp44, perforin by NK cells of peripheral blood, decrease of cytotoxicity, increase of expression of inhibiting receptor KIR2DL1 [27]. In the experiments *in vitro*, the TGF-β secreted by decidual cells causes reduction of CD16 expression by NK cells of peripheral blood, approximating their phenotype to decidual NK cells [5, 17]. Probably, decidual NK cells can maintain their differentiation due to autocrine impact of cytokine TGF-β, because, according to literature data, during pregnancy the number of decidual NK cells, characterized by capacity to secrete TGF-β, increases [31].

At the same time, probably, not all NK cells of peripheral blood can migrate into the uterus and change their phenotype. It was demonstrated that among decidual cells compared to NK cells of peripheral blood many more cells expressed receptor CD25 [33]. At that, more than half of cells present in decidua and expressing CD25 are NK cells, while in peripheral blood, T-lymphocytes make up the majority of $CD25^+$ cells [33]. For NK cells of peripheral blood with $CD3^-CD56^{bright}CD25^+$ phenotype the reduced expression of inhibiting receptors and increased expression of activation receptors is typical, as well as reduced content of perforin and granzyme B and increased expression of IFNγ and TGF-β [33]. It is supposed that these NK cells can migrate into the uterus and their main function is to secrete cytokines and maintain cytokine microenvironment in the zone of uteroplacental bed at pregnancy [33]. However, at



BM – bone marrow; SLT – secondary lymphoid tissue; PB – peripheral blood; SP – spleen; LN – lymph nodes; L – liver; EM – endpmetrium; D – decidua; CMV – cytomegalovirus

Figure 1. Peculiarities of CD56^{dim} and CD56^{bright} NK cells differentiation

incubation of CD25$^+$ NK cells with trophoblast, NK cells increased expression of NKp30, NKp44, NKp46 receptors [33], which indicates induction of CD25$^+$ NK cell activation by trophoblast.

In uterus mucous membrane, the presence of NK cell progenitors at the intermediate stage of differentiation was determined, while no NK cell progenitors at early stages of differentiation were found [21]. Uterus NK cell progenitors at the intermediate stage have phenotype CD45$^+$CD3$^-$CD19$^-$CD117$^+$CD94$^-$CD7$^{+/-}$CD69$^+$CD122^{dim}CD127$^{+/-}$NKp44$^{+/-}$NKG2D$^-$ [21], which makes them similar to NK cell progenitors at the intermediate stage present in secondary lymphoid tissue [10, 13, 37]. Furthermore, NK cell progenitors at the intermediate stage in uterus [21], like in secondary lymphoid tissue [12], can secrete IL-22, which indicates the occurrence of NK cell differentiation process in uterus not only from NK cells of peripheral blood after migration, but also from NK cell progenitors placed in uterus.

Thus, uterine NK cells represent the terminal stage of NK cell differentiation, which resemble the stage of CD56^{bright} NK cell differentiation. For uterine NK cells expression of CD56, NKp46, NKG2D, NKp30, NKp44, secretion of IFNγ and TGF-β is typical. Without pregnancy, endometrial NK cells are present in the uterus; following pregnancy endometrial NK cells change their phenotype and differentiate into decidual NK cells. Significant growth of decidua NK cell numbers at pregnancy takes place through migration of NK cells from peripheral blood and respective alteration of their phenotype although differentiation of uterine NK cells can also occur *in situ*. Figure 1 shows paths of differentiation of CD56^{dim} and CD56^{bright} NK cells.

Conclusion

Currently, there is a great deal of evidence on phenotypic peculiarities of NK cells, which can determine functional features of different populations of NK cells. Summarizing these phenotypical and functional characteristics of NK cells populations can help in further distinguishing stages of NK cells differentiation process. Determining NK cell differentiation markers and examining peculiarities of NK cell functional characteristics promoted discovering NK cell capacity for pre-activation and retention of this condition during a long period of time. Further investigation of so-called pre-activated NK cells, or memory-like NK cells, may contribute in understanding of fundamental immunologic processes. Appearance of data about possible non-linear nature of NK cell differentiation, as well as about influence of microenvironment cells on NK cell differentiation process, indicates the necessity of further investigations in this direction. Examining expression patterns of NK cell receptors at pregnancy is of special interest, as in this case, discovering reversibility of NK cell differentiation at the final stages of this process is possible, as well as the dependence of uterus NK cell functional peculiarities from the repertoire of expressed receptors. Further study and analysis of peculiarities of the NK cell functional state will allow us to come close to understanding the NK cell role at pregnancy and disorder of NK cell regulation in the zone of uteroplacental bed at pathologic pregnancy.

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Авторы:

Михайлова В.А. *— к.б.н., научный сотрудник лаборатории межклеточных взаимодействий отдела иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта»; ГБОУ ВПО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, кафедра иммунологии, Санкт-Петербург, Россия*

Белякова К.Л. *— лаборант-исследователь лаборатории межклеточных взаимодействий отдела иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта», Санкт-Петербург, Россия*

Сельков С.А. *— д.м.н., профессор, заслуженный деятель науки, заведующий отделом иммунологии и межклеточных взаимодействий 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 отдела иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии имени Д.О. Отта»; ГБОУ ВПО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, кафедра иммунологии; ведущий научный сотрудник отдела иммунологии ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия*

Authors:

Mikhailova V.A.*, PhD (Biology), Research Associate, Laboratory of Cell Interactions, Department of Immunology and Cell Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology; Pavlov First St. Petersburg State Medical University, Department of Immunology, St. Petersburg, Russian Federation*

Belyakova K.L.*, Laboratory Assistant, Laboratory of Cell Interactions, Department of Immunology and Cell Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg, Russian Federation*

Selkov S.A.*, PhD, MD (Medicine), Professor, Honored Scientist, Head, Department of Immunology and Cell Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology, St. Petersburg, Russian Federation*

Sokolov D.I.*, PhD, MD (Biology), Head, Laboratory of Cell Interactions, Department of Immunology and Cell Interactions, D. Ott Research Institute of Obstetrics, Gynecology and Reproductology; Pavlov First St. Petersburg State Medical University, Department of Immunology; Leading Research Associate, Department of Immunology, Institute of Experimental Medicine, St. Petersburg, Russian Federation*

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