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РОЛЬ РАЗЛИЧНЫХ СУБПОПУЛЯЦИЙ CD8⁺Т-ЛИМФОЦИТОВ ПРИ БЕРЕМЕННОСТИ

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Резюме. В настоящее время выявлено существование широкого спектра субпопуляций CD8⁺Т-лимфоцитов, среди которых выделяют субпопуляции наивных клеток, клеток памяти, регуляторных. Кроме клеток с высоким уровнем цитотоксической активности, выявлены субпопуляции, обладающие выраженной регуляторной активностью. Каждая субпопуляция характеризуется совокупностью продуцируемых медиаторов, поверхностных и внутриклеточных маркеров, позволяющих предположить их различную функциональную активность в условиях *in vivo*. В настоящем обзоре описана классификация CD8⁺Т-лимфоцитов, учитывающая их морфофункциональные признаки. Традиционно считается, что CD8⁺Т-лимфоциты являются популяцией лимфоцитов, обладающей высокой цитотоксической активностью, что имеет чрезвычайное значение в условиях инвазии полуалогенных плодовых клеток в эндометрий при беременности. Доля CD8⁺Т-лимфоцитов в децидуальной оболочке довольно велика. В обзоре обсуждаются известные на сегодняшний день механизмы регуляции дифференцировки, избирательной миграции и функциональной активности CD8⁺Т-лимфоцитов в децидуальной оболочке и плаценте при беременности. Основными факторами цитотоксического действия CD8⁺Т-лимфоцитов являются перфорин и гранзим. К регуляторным медиаторам CD8⁺Т-лимфоцитов относят цитокины IL-2, IL-5, IL-13, IFNγ, IL-17, TGF-β и IL-10. Для развития эффекторных свойств CD8⁺Т-лимфоцитов необходима антигенная стимуляция, которую обеспечивает взаимодействие CD8⁺Т-лимфоцитов с активированными CD4⁺Т-лимфоцитами или дендритными клетками, воздействие цитокинов. Условия специфической дифференцировки CD8⁺Т-лимфоцитов формируются за счет различного характера микроокружения. В децидуальной оболочке при беременности наблюдается концентрация CD8⁺Т-лимфоцитов, но их фенотип и функциональнальная активность отличаются от CD8⁺Т-лимфоцитов периферической крови. В настоящее время продолжается изучение механизмов избирательной миграции CD8⁺Т-лимфоцитов с регуляторными свойствами в децидуальную оболочку. Полагают, что это обеспечивается при участии хемокиновых рецепторов CXCR3 и CCR5, цитокинов IL-6 и IL-15. Характер активности CD8⁺Т-лимфоцитов и продукция ими цитокинов CSF2, IFNγ, IL-1β, IL-2, IL-6, IL-8,IL-10, IL-12 и TNFα в децидуальной оболочке имеют решающее значение для успешной инвазии клеток трофобласта. В свою очередь, клетки трофобла-

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ста и плаценты способствуют формированию пула регуляторных CD8+Т-лимфоцитов в децидуальной оболочке, способны индуцировать апоптоз CD8+Т-лимфоцитов. Таким образом, взаимодействие CD8+Т-лимфоцитов матери и трофобласта в зоне маточно-плацентарного контакта является важным звеном в формировании иммунологической толлерантности в системе мать-плод.

Ключевые слова: Т-лимфоциты, беременность, цитотоксичность, децидуальная оболочка

THE ROLE OF SUBPOPULATIONS OF CD8+ T LYMPHOCYTES IN THE DEVELOPMENT OF PREGNANCY

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Abstract. At the present time, a broad spectrum of CD8+ T lymphocyte subsets is revealed, including naïve cells, memory cells and regulatory subpopulations. Along with cells with high cytolytic activity, some subsets with marked regulatory activity were found there. Each subpopulation is characterized by a set of produced mediators, surface and intracellular markers allowing to suggest their differential *in vivo* functional activity. The present review article proposes a classification of CD8+ T cells which takes into account their morphological and functional features. According to conventional view, the CD8+ T lymphocytes is a cell population exhibiting high cytotoxic ability which is of critical significance in pregnancy, under the conditions of semi-allogenic fetal cell invasion into the endometrium. The fraction of CD8+ T cells is rather high in decidual structures. The review discusses the known mechanisms of differentiation regulation, selective migration and activity of CD8+ T cells in decidual membrane and placenta in the course of pregnancy. Perforine and granzyme are the main cytotoxicity factors of CD8+ T cells. IL-2, IL-5, IL-13, IFNγ, IL-17, TGF-β and IL-10 cytokines are considered regulatory mediators of CD8+ cells. To induce the effector properties of CD8+ T cells, an antigenic stimulation is required, which is provided by interactions between the CD8+ T cells and activated CD4+ T cells or dendritic cells, cytokine effects. Specific differentiation of the CD8+ T cells is determined by differences in microenvironvent. In the course of pregnancy, accumulation of CD8+ T cells is observed in decidual membrane, but their phenotype and functional properties differ from CD8+ T cells in peripheral blood. At present time, the mechanisms of selective CD8+ T cell migration to decidual membrane are studied. These events are suggested to be mediated by means of CXCR3 and CCR5 chemokine receptors, IL-6 and IL-15 cytokines. The features of CD8+ T cell activities, and production of some cytokines, e.g., CSF2, IFNγ, IL-1β, IL-2, IL-6, IL-8,IL-10, IL-12 and TNFα in decidual membrane and is of critical significance for effective invasion of trophoblast cells. In turn, the trophoblast and placental cells promote development of regulatory CD8+ T lymphocytes in decidual membrane, being able to induce CD8+ T cell apoptosis in decidual membrane. Hence, interaction between the maternal CD8+ T cells and trophoblast in the area of uterine-placental contact is an important link during development of immunological tolerance in the maternal/fetal system.

Keywords: T lymphocytes, pregnancy, cytotoxic, decidua

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Introduction

Cytotoxic lymphocytes are one of the key cellular elements, whose action is aimed at viral clearance. However, the spectrum of their function is much wider. It is noted that the change in metabolic pathways and function of CD8+ T lymphocytes is associated with aging of the organism [46]. In connection with the possibility of recognition of MHC I, CD8+ T lymphocytes are an important part of the antitumor immune response. In particular, activated CD8+ T lymphocytes control cell growth in solid tumours [23]. CD8+ T lymphocytes are involved in many pathological processes, for example, in nerve fibre damage in multiple sclerosis [133], cerebral vasculature in cerebral malaria [126], bronchial asthma [95], rheumatoid arthritis [16] and immunopathology in skin leishmaniasis [94]. In the host graft system,

the effect of $CD8^+$ T lymphocytes is also crucial for engraftment of the graft [5, 112, 151].

Pregnancy is a unique example of the coexistence of genetically diverse tissues. In this case, the placenta is not an absolute barrier to the cells of the immune system of the mother: there is a mutual penetration of the cells of the mother and foetus – the phenomenon of microchimerism, which can both positively and negatively affect the outcome of pregnancy [101, 108]. T lymphocytes are of great importance for the recognition and elimination of foreign genetic material in the body, however, in the case of physiological pregnancy, there is no attack from the mother's immune system – explained by the immunological tolerance for the foetus. At present, the mechanisms of the development of this tolerance are intensively studied. In the endometrium and decidua, a change in the $CD8^+$ T lymphocyte content is observed when pregnancy occurs compared with non-pregnant women and obstetric pathologies compared to the physiological course of pregnancy, but the role of these cells has not been sufficiently studied. It has been established that along with $CD8^+$ T lymphocytes possessing cytotoxic action, there are $CD8^+$ T lymphocytes with regulatory properties, as well as several subpopulations of memory cells. $CD8^+$ T lymphocytes probably play one of the most important roles in the preservation or rejection of the foetus. At the present time, however, the whole spectrum of $CD8^+$ T lymphocyte subpopulations is insufficiently characterized and the role of these cells in maintaining a physiological pregnancy is not fully understood.

Phenotype and functional activity of $CD8^+$ T lymphocytes

For a long time, $CD8^+$ T lymphocytes have been considered a homogeneous population. At present, it has become clear that the diversity of $CD8^+$ T lymphocyte subpopulations is determined by their differences both in phenotype, and in functional purpose, and in the characteristics of intercellular interactions. The vast majority of $CD8^+$ T lymphocytes express the transcription factors T-bet and STAT4 and secrete the cytokines IFNγ and TNFα [93]. The main factors of the cytotoxic effect of $CD8^+$ T lymphocytes are perforin and granzymes [93]. In addition, $CD8^+$ T lymphocytes express a rather wide spectrum of receptors characteristic for NK cells: KIR – CD158a/h, CD158bj, CD94, NKG2A, NKG2C [132].

Several different subpopulations of $CD8^+$ T lymphocytes are described in the public sources. The earliest classification of these lymphocytes is based on the spectrum of cytokines secreted by them. According to this classification, $CD8^+$ T lymphocytes can be divided into 3 subpopulations: Tc1 – producing IFNγ and not producing IL-4; Tc2 – not producing IFNγ, producing IL-4; and Tc0 – producing IFNγ and IL-4 [90, 138]. The majority of $CD8^+$ T lymphocytes of human peripheral blood (80%) belongs to Tc1 [138]. Tc1 secrete IL-2, IFNγ, small amounts of IL-5, IL-13, and express the transcription factors T-bet and Hlx. Tc2 and Tc0 secrete IL-4, IL-5, IL-10, IL-13 [138]. Tc2 express the transcription factors GATA3 and Hlx [83]. Tc0 and Tc2 are characterized by high expression of CD30, CD40L, CD28, whereas Tc1 have a low expression of these molecules [138]. Tc2 are identified by the expression of the CRTH2 marker. The cytotoxic activity of the three subpopulations of $CD8^+$ T lymphocytes is not different [138]. At the functional level, Tc1 accumulates faster in the lymph nodes and promotes a faster development of the immune response, and they are more apoptotic after activation (the mechanism does not involve changes in Fas and FasL expression) than Tc2 [128, 138]. Cytokine IL-4 stimulates the development of IL-4-producing subpopulations, suppressing production of IFNγ [138]. The effect of IL-4 results in a loss of ability of Tc1 to secrete IL-2, and hence a loss of ability to spontaneously proliferate [111]. IL-12 inhibits the production of IL-5, IL-4 and IL-10, but stimulates the production of IFNγ, stimulates the development of the Tc1 subpopulation [138]. Subpopulations of Tc0 and Tc2 are not affected by IL-12 or IL-4 [138]. Prostaglandin E2 promotes a shift in the equilibrium toward Tc2 [10]. Due to the secretion of various cytokines, Tc can change the direction of differentiation of $CD4^+$ T lymphocytes. Currently, there are still studies using this classification.

In the most frequently used classification, $CD8^+$ T lymphocytes are divided depending on the expressed markers on naïve ($CD45RA^+$ $CCR7^+$), effector ($CD45RA^+CCR7^-$), effector memory cells ($CD45RA^-CCR7^-$) and memory cells ($CD45RA^-$ $CCR7^+$) [130]. Naïve $CD8^+$ T lymphocytes have the phenotype $CD44^{low}$; when activated, the expression of this marker increases [22]. Depending on the expression of CD28 and CD27, effector cells and memory effector cells are divided into the following subpopulations: EM1 ($CD28^+CD27^+$), EM2 ($CD28^-CD27^+$), EM3 ($CD28^-CD27^-$), and EM4 ($CD28^+CD27^-$) [130].

During the immune response, $CD8^+$ T lymphocytes form memory cells, which are divided into three types: resident, effector and central [70]. Resident memory $CD8^+$ T lymphocytes are localized in non-lymphoid tissues (mucous membranes and reproductive tract), differ in the inability to leave tissues in circulation and are characterized by the

phenotype $CD8^+CD103^+CD69^+$ [70, 124]. Effective $CD8^+$ T memory lymphocytes can migrate between tissues and secondary lymphoid organs, they do not express homing molecules that determine migration to the lymph nodes [124], are characterized by the $CD8^+CD45RO^+CD62L^-CCR7^-$ [70] phenotype, high expression of cytolytic enzymes [130], high expression of transcription factor GATA3, high level of expression of IL-6Rα, IL-7Rα and increased level of proliferation [74]. Under the *in vitro* conditions, it was shown that after activation (CD3/CD28), these cells also produce cytokines IL-2, IL-5, IL-13 and IFNγ [74]. In the experiment, it was shown that the proliferation of effector $CD8^+$ T lymphocytes is stimulated by IFNγ, with the synergistic action of IL-6 and IL-15 [74]. Also, the proliferation of effector $CD8^+$ T lymphocytes can support IL-2 (autocrine). Cytokines secreted by effector memory $CD8^+$ T lymphocytes are involved in antiviral and antibacterial defence of the body, in addition, there is an increase in the content of these cells in autoimmune processes (bronchial asthma) [74]. Central memory $CD8^+$ T lymphocytes are localized in secondary lymphoid organs, they express homing molecules that determine migration to the lymph nodes, have a $CD8^+CD45RO^+CD62L^+CCR7^+$ phenotype and a high proliferative potential upon re-encounter with antigens [70, 124].

By analogy with $CD4^+$ lymphocytes, Tc17 producing IL-17 are isolated. They are characterized by the phenotype $CD27^-CD28^+CD45RA^-CCR5^+CCR6^+$, secretion of cytokines IL-17, IFNγ [68]. A subpopulation of $CD8^+$ non-cytotoxic IL-17-producing T lymphocytes (Tcn17) is also formed, which is formed in the presence of TGF-β and IL-6 [83]. This subpopulation is characterized by the expression of the transcription factor Th17 RORγt, reduced expression of the transcription factors GATA3, T-bet, Hlx, the lack of production of IFNγ, granzyme B, IL-10 and the absence of cytolytic activity [83].

$CD8^+$ regulatory T lymphocytes ($CD8^+$ Treg) are a population of cells newly identified and are currently intensively studied. Along with $CD4^+$ Treg, $CD8^+$ Treg are important for the formation of immunological tolerance [84]. Their presence in immunologically privileged organs, participation in many pathologies of immune genesis, as well as their key role in the host-transplant reaction have been described. For $CD8^+$ Treg, the expression of CTLA-4, CD25, HLA-DR, CD45RA, CCR7, CD62L, CD28, CD101, CD103, CD122, TcRα/β, ICOS, FOXO1 and HELIOS, IL-2ra, CCR4, GARP, IL-10 and TGF-β [2, 7, 37, 55, 75, 84, 119]. Expression of these molecules is important both for maintaining the $CD8^+$ Treg population and for manifesting their functional activity against other cells [55]. According to some data, $CD8^+$ Treg does not express CTLA-4, FasL [119]. $CD4^+$ T lymphocytes requires the expression of FoxP3 for the implementation of regulatory properties [39, 121, 148]. Depending on the expression of FoxP3 $CD8^+$ Treg can be divided into $CD8^+FoxP3^+$ and $CD8^+FoxP3^-$ subpopulations. For $CD8^+FoxP3^+$Treg, CD62L expression is also characteristic. Phenotype $CD8^+$ FoxP3- Treg is characterized by the expression of CD103, which is crucial for the formation and implementation of suppressive properties of $CD8^+$ Treg lymphocytes, especially for the subpopulation of $CD8^+$ FoxP3 cells [75, 84]. There are data on intracellular expression of FoxP3, characteristic of $CD8^+$ Treg of lymphocytes [7, 55]. Expression of surface molecules is largely specifically regulated by various microRNAs [55]. Probably, the formation of two subpopulations ($CD8^+FoxP3^+$ and $CD8^+FoxP3^-$ Treg) is associated with the action of TGF-β (in conjunction with the activation of the T cell receptor) and IL-10 [37, 84]. Both subpopulations have a low expression of perforin and granzymes, intracellular expression and secretion of IL-10, and their suppressive effect is not due to cytotoxic effects, but to the production of TGF-β and IL-10 and contact interactions involving the CTLA-4 molecule [55, 84, 119].

Thus, the population of $CD8^+$ T lymphocytes is a collection of cells quite diverse in phenotype and function. The conditions for differentiation of $CD8^+$ T lymphocytes are also different.

Differentiation of $CD8^+$ T lymphocytes

Recent thymic emigrants that have just emerged from the bone marrow are localized in the blood and spleen, and differ from mature naïve cells: they have a decreased secretion of immunoregulatory cytokines, reduced expression of CD62L, CXCR4, granzyme B, reduced cytotoxicity, the ability to rapidly proliferate with an immune response and provide antiviral protection [27]. It is believed that decidual $CD8^+$ T lymphocytes refer to such recent thymic emigrants at the periphery, but this issue has not been studied enough.

The antigen-independent differentiation of $CD8^+$ T lymphocytes occurs in the thymus, from where the naïve cells exit into the periphery. In addition, naïve $CD8^+$ T lymphocytes undergo antigen-dependent differentiation in secondary lymphoid organs: in the lymph nodes [15, 135] and in the spleen [11], naïve $CD8^+$ T lymphocytes interact with dendritic cells (DC) via the $XCR1^+$ molecule in the presence of secreted IL-15, and also in the presence of $CD4^+$ T lymphocytes secreting IL-2 [70]. Naïve $CD8^+$ T lymphocytes are located in the paracortical area of the lymph node [63].

In secondary lymphoid organs, $CD8^+$ T lymphocytes, along with DC, contribute to the activation of $CD4^+$ T lymphocytes [11]. The interaction of $CD8^+$ T lymphocytes with $CD4^+$ T helper cells is not necessarily accompanied by detachment from DC [11]. Further, the aggregate migrates into the white pulp of the spleen [11].

After activation, $CD8^+$ T lymphocytes can differentiate into short-living effector cells that attack infected cells and die as a result of apoptosis after performing their function, or differentiate into circulating central memory cells [9]. About 5-10% of activated $CD8^+$ T lymphocytes are transformed into memory cells [9]. Central memory cells are localized mainly in the interfollicular region of the lymph nodes [63]. $CD8^+$ T lymphocytes are stored in the lymph nodes due to the expression of the homing receptors CCR7 and CD62L (L-selectin) [131].

Developing the effector properties of $CD8^+$ T lymphocytes requires a triple signal: antigen stimulation through TcR, a costimulatory signal from CD28, microenvironment – exposure to cytokines IL-12, IFNα, IFNβ [24, 88]. IL-12 and IFN type I cytokines play an important role both for the formation of a pool of effector cells and for the formation of memory cells [147]. These cytokines promote differentiation mainly into the Tc1 subpopulation [90]. The effect of cytokines causes a change in the expression of hundreds of genes responsible for proliferation, cytotoxic lymphocyte effector activity, survivability, migration, a wide range of transcription factors (including T-bet and Blimp-1) [24]. Secreted on the first day after activation of naïve $CD8^+$ T lymphocytes, IFNγ via autocrine action activates and differentiates $CD8^+$ T lymphocytes into cytotoxic T lymphocytes, stimulates the expression of the transcription factor T-bet, granzyme B production and plays an important role in early activation [22]. The effect of IFNγ is synergistically enhanced by the action of IFNα and IFNβ, but it does not matter for the differentiation of naïve $CD8^+$ T lymphocytes in the presence of IL-12 [22].

The interaction of $CD8^+$ T lymphocytes with activated $CD4^+$ T lymphocytes, DC, is important for the formation of a pool of memory $CD8^+$ T lymphocytes, as well as the effect of cytokines. The interaction of $CD8^+$ T lymphocytes with DC is exercised through the CD70 molecule on the DC and CD27 on the surface of $CD8^+$ T lymphocytes, and the interaction of CD40L on activated $CD4^+$ T lymphocytes with CD40 on DC is simultaneously observed [50]. The expansion of memory $CD8^+$ T lymphocytes depends on the interaction with CD4 T helper cells via CD40/CD40L and minor histocompatibility molecules [109]. The kinetics of cellular interaction remains a debating point [50]. It is believed that there is also a reserve pathway for maintaining memory cell differentiation, which is relevant in the absence of IL-12 and IFN type I, but it is not yet identified [147].

In the absence of $CD4^+$ T lymphocytes, naïve $CD8^+$ T lymphocytes cannot activate into effector cells, whereas memory $CD8^+$ T lymphocytes can proliferate and differentiate into effector cells [76].

The IL7R, IL2R, IL15R, microRNA (miR)-155 receptors play an important role in determining the direction of differentiation of $CD8^+$ T lymphocytes in the direction of the effector or memory cells, as well as the nature of the activation of TcR, in particular, the impact through the molecules of diacylglycerol (DAG), DAG kinase (DGK) α and ζ [8, 60, 113, 131, 150]. Deletion of DGK α and ζ leads to a decrease in the number of memory cells. This effect can be detected by observing a decrease in $CD8^+$ expression by T lymphocytes of CD127, CD62L expression, as well as disturbance of the homeostasis of a subpopulation of memory cells and their viability [150]. Also, the deletion of DGK α and ζ causes a decrease in $CD8^+$ T lymphocyte expression of the chemokine receptors CCR4, CCR5 and CXCR3, responsible for migration to the lymph nodes during the immune response [150].

$CD8^+$ T regulatory lymphocytes can differentiate from naïve or effector $CD8^+$ T lymphocytes in both the thymus and periphery [2]. As in the case of $CD4^+$ Treg cells, TGF-β is important in the formation of the $CD8^+$ Treg subpopulation: it suppresses the cytotoxic activity of $CD8^+$ lymphocytes [127] by inducing microRNAs, leading to suppression of IFNγ production [17, 84]. The effect of TGF-β was also manifested in the increased expression of CTLA-4, ICOS by the $CD8^+$ T lymphocytes, and the CD62L on the $FoxP3^+$ subpopulation of $CD8^+$ T lymphocytes, but molecule CD103 on the subpopulation of $CD8^+FoxP3^-$ T lymphocytes [75, 84]. TGF-β-induced $CD8^+FoxP3^+$ and $FoxP3^-$ cells reduce production of IFNγ and do not proliferate in response to IL-2 [84]. The effect of monoclonal anti-CD3 antibodies with *in vitro* conditions leads to the induction of differentiation and expansion of $CD8^+CD25^+FoxP3^+$ Treg lymphocytes [32]. Mesenchymal stem cells (MSC) of the placenta promote the differentiation of the $CD8^+$ Treg lymphocytes ($CD8^+IL\text{-}10^+$) with the participation of the PDL2 molecule (anti-programmed death ligand-2) [77]. IFNγ and TNFα stimulate the expression of PDL2 on placental MSC and differentiation of $CD8^+IL\text{-}10^+$ lymphocytes [77].

Thus, $CD8^+$ T lymphocytes are capable of differentiation both in the thymus and in the periphery. The direction of differentiation depends on the nature of the intercellular interactions within the antigen presentation process in conjunction with the action

of soluble factors. The mechanisms of regulation of differentiation of $CD8^+$ T lymphocytes, in particular at the periphery, have not been sufficiently studied. After differentiation, $CD8^+$ T lymphocytes acquire the ability to specifically migrate to further their function.

Migration of $CD8^+$ T lymphocytes to the decidua

$CD8^+$ T lymphocytes are present in peripheral blood, endometrium of non-pregnant women and in the decidua during pregnancy. There is little data on migration mechanisms of $CD8^+$ T lymphocytes. However, several specific molecules can be isolated, whose expression promotes selective migration of cytotoxic lymphocytes into the decidua. Migration of $CD8^+$ T lymphocytes to the decidua is facilitated by an increase in the expression of CXCR3 [21] and CCR5 [63, 93]. CXCR3 ligands produce decidual stromal cells: CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC) [30]. CXCL9 is expressed in the placenta and in the chorioamniotic membrane, is found in the bloodstream, and the increased production of this molecule is associated with premature delivery and low foetal weight [29, 62, 65, 105, 115]. The increased CXCL11 content in amniotic fluid in the second trimester of pregnancy is associated with premature delivery [30] and may be associated with the involvement of $CD8^+$ T lymphocytes by enhancing their migration. CCR5 ligands are CCL3 (MIP-1α), CCL4 (MIP-1β), RANTES. CCL4 is produced by decidual stromal cells [30], and CCL3 is expressed in the placenta by trophoblast, endothelial cells [1]. RANTES is produced by the decidua [28] and the placenta [47]. Trophoblast produces MIP-1α and RANTES, CCL3 [54, 99].

The decidua is observed to be the producer of IL-15 [96]. Migration of $CD8^+$ memory cells largely depends on the binding of P- and E-selectins, the expression of which increases in the presence of IL-15 [66]. $CD8^+$ T lymphocytes are characterized by expression of the CXCR6 receptor, which, through interaction with the chemokine CXCL16 secreted by trophoblast, attracts T lymphocytes to the decidua [52]. CD103 expression can be associated with the migration of $CD8^+$ Treg into the inflammation zone [56, 84]. In the placenta, the CD103 ligand – E-cadherin, is expressed by the villous trophoblast and is important for the functioning of the trophoblast itself [14, 78, 81], as well as the decidua [33, 154]. Expression by villous and extravillous trophoblast, endometrial cells of prostaglandin D2 can cause specific migration to the decidua (to the implantation site of the foetal egg) of Tc2 lymphocytes due to their expression of CRTH2 [89].

When endometrial cells are differentiated into decidual cells, the expression of CXCL9 (MIG), CXCL10 (IP10), CXCL11 (ITAC) and CCL5 (RANTES) is suppressed, which leads to a decrease in Tc1 involvement in the decidua compared to the endometrium of non-pregnant women [35]. This can be one of the mechanisms of formation of immunological tolerance in the mother-foetus system.

If there is an infection, the migration of $CD8^+$ T lymphocytes to the decidua increases, activation of $CD8^+$ T lymphocytes occurs and immunological aggression against the foetus without elimination of the pathogen develops due to the action of $CD8^+$ T lymphocytes [21]. Expression of E-cadherin with syncytiotrophoblast during preeclampsia is enhanced in comparison with physiological pregnancy [53, 81], which may contribute to excessive involvement of $CD8^+$ T lymphocytes to the placenta.

Cytokine IL-6 plays an important role in the formation and development of pregnancy, is found in significant amounts in the stroma of the decidua, trophoblast and endothelium of the spiral arteries. It has been established that IL-6 promotes the proliferation and differentiation of $CD8^+CD25^+FoxP3^+$ Treg, an increase of their share in the blood stream and, as a result, an increase in their migration to the decidua [42, 56, 92], which can significantly contribute to the formation of immunological tolerance of mother's immune system in relation to the foetus and the development of the placenta [102], as well as in the process of rejection of the foetal tissues during the delivery [97].

In the endometrium of non-pregnant women, the proportion of $IFN\gamma^+CD8^+$ T lymphocytes reaches 25% of all $CD8^+$ T lymphocytes; in spontaneous abortions, there is a significant decrease in the content of $IFN\gamma^+CD8^+$ T lymphocytes in the decidua compared with the endometrium of non-pregnant women (less than 11% of $CD8^+$ T lymphocytes) [31], which indicates the important role of $CD8^+$ T lymphocytes in implantation and the establishment of pregnancy.

Currently, there is no consensus on the persistence of the population of cytotoxic lymphocytes in the decidua during pregnancy. Some authors claim that during the pregnancy, the amount of $CD8^+$ T lymphocytes in the decidua of women does not change [145] and is 45-75% of the T lymphocytes of the decidua (T lymphocytes constitute 10-20% of decidual leukocytes) [34, 52, 93]. Other authors point out a different content of cytotoxic lymphocytes in the decidua, depending on the period of pregnancy. In the first trimester of pregnancy, the proportion of $CD8^+$ T lymphocytes in the decidua is insignificant and is 2-7% of the $CD45^+$ cells, while in the third trimester of pregnancy it is up to 30% [21]. Such a difference in the data obtained by the authors on the content of T lymphocytes in the decidua can be associated with the absence of standardized methods for isolating cells from the decidua.

The ratio of T cell populations in the systemic blood stream and decidua is different. In the decidua, the $CD8^+$ T lymphocyte count is 62%, and $CD4^+$ is 33% [91] of the total number of T lymphocytes, whereas in the peripheral blood, the proportion of $CD8^+$ lymphocytes is 21%, and 75% of $CD4^+$ lymphocytes [91]. The number of $CD8^+$ memory T lymphocytes in the decidua considerably exceeds their number in peripheral blood [134], and the proportion of naïve $CD8^+$ T lymphocytes is much lower than in peripheral blood [130], which indicates the presence of predominantly differentiated cells. Decidual $CD8^+$ T lymphocytes have a lower degree of expression of perforin and granzyme B compared to $CD8^+$ T lymphocytes of peripheral blood, and a small number of $CD8^+$ T lymphocytes expressing granzyme B [130] (Table 1).

With pathologies of pregnancy, there is a change in the content of $CD8^+$ T lymphocytes in the blood and decidua. Thus, with preeclampsia, a decrease in $CD8^+FoxP3^+$ T lymphocytes ($CD8^+$ T regulatory cells) in peripheral blood of women has been observed [152]. Spontaneous abortion shows an increased $CD8^+$ lymphocyte count in the decidua [6]. The development of chronic chorioamnionitis in pregnant women is accompanied by an increase in the cytotoxic activity of $CD8^+$ T lymphocytes, characterized by the phenotype $CD300a^+CD8^+$, in the systemic blood flow compared to women with a physiological pregnancy [64].

Thus, $CD8^+$ T lymphocytes play one of the decisive roles in the physiological and pathological development of pregnancy. Not only the existence of specific migration mechanisms of various subpopulations of $CD8^+$ T lymphocytes in the endometrium and decidua is observed, but their concentration in these tissues in comparison with peripheral blood. At the same time, the ratio of various subpopulations of $CD8^+$ T lymphocytes in the decidua at various stages of development of pregnancy is substantive.

Phenotypic and functional features of $CD8^+$ T lymphocytes of the decidua

The presence of $CD8^+$ T lymphocytes in the endometrium is important for the implantation of the

TABLE 1. CHARACTERISTICS OF SUBPOPULATIONS OF DECIDUAL $CD8^+$ T LYMPHOCYTES

Subpopulation of decidual $CD8^+$ lymphocytes		Surface markers	Intracellular markers	Secreted cytokines	Share in the decidua
naïve		$CD8^+$, $CD45RA^+$, $CCR7^+$, $CD62L^+$, $CD45RO^-$ [87], $CD27^+$, $CD28^+$ [131], $CD44^{low}$ [22]	T-bet and STAT4 [93]	IFNγ, TNFα [93]	3% [131]
Memory cells	Resident memory cells	$CD8^+CD45RO^+CD103^+CD69^+$ [70, 136]			
	Central memory cells	$CD8^+$,$CD45RO^+$, $CCR7^+$, $CD62L^+$, $CD45RA^-$, $CD27^+$, $CD28^+$ [70]	$Eomes^{low}$ [87]		2% [131]
	Memory cells (memory effector cells)	$CD8^+$, $CD45RO^+$, $CD62L^-$, $CCR7^-$ [70], $CD45RA^-$ [131], IL-6Rα$^+$, IL-7Rα$^+$ [41, 74], $CD103^+ICOS^+$, $CD69^+$, HLA^-DR^+ [91, 129, 130, 134]	GATA3 [74], $Tbet^+$, $Eomes^+$ [87]	Contradictory data on the production of cytolytic enzymes (increased [130], reduced expression of granzyme B and perforin [134]) IL-2, IL-5, IL-13, IFNγ [74]	65% [131]
Effector T lymphocytes		$CD8^+$, $CD45RA^+$ [131], $CD45RO^-$ [87], $CD62L^-$, $CCR7^-$ [41]	$T\text{-}bet^+$ [87]	Reduced expression of granzyme B and perforin	13% [131]
CD8-suppressor (regulatory) cells		$CD8^+CD28^-$, $CD69^+$, HLA^-DR^+ [129], $CD103^{+/-}$, $CD62L^{+/-}$, $CD25^+$, HLA^-DR^+, $CD45RA^+$, $CCR7^+$, $CD28^+$, $CD101^+$, $CD122^+$, TcRα/β$^+$, $ICOS^+$, $FOXO1^+$, $HELIOS^+$, $IL\text{-}2RA^+$, $CCR4^+$, $GARP^+$ [2, 7, 37, 55, 75, 84, 119]	$FoxP3^{+/-}$ [41] Vbeta 9 [119]	CCR4, IL-10 and TGF-β [2, 7, 37, 55, 75, 84, 119] IL-10, low expression of perforin and granzyme	
Tc17		$CD27^-$, $CD28^+$, $CD45RA^-$, $CCR5^+$, $CCR6^+$ [18]		IL-17, IFNγ [68]	

ovum. Cells of the Tc2 subpopulation predominate in the implantation site. They express CRTH2, which is an additional receptor of prostaglandin D2 and is characteristic of Th2 [89]. The cytolytic activity of $CD8^+$ T lymphocytes is hormone-dependent: it is present in the proliferative phase of the menstrual cycle and is absent in the secretory phase [142].

Decidual $CD8^+$ T lymphocytes differ in phenotype and functional characteristics from peripheral blood lymphocytes (Table 1). In the bloodstream, naïve $CD8^+$ T lymphocytes predominate [131]. Decidual and placental $CD8^+$ T lymphocytes in the vast majority are activated effector cells or effector memory T cells [131] (Table 1). Activated effector cells are characterized by the phenotype $CD45RA^+$, $CD45RO^-$, $CD62L^-$, $CCR7^-$, expression of Tbet transcription factor [41, 87, 131]. Effector memory cells are characterized by the phenotype $CD8^+CD45RA^-CCR7^-CD28^-$ $CD45RO^+CD103^+ICOS^+$, increased expression of CD69 and HLA-DR and lack of perforin. Whereas in the peripheral blood, naïve CD8 T cells ($CD8^+CD45RA^+CD45RO^-CCR7^+$) predominate [91, 129, 130, 134]. Also for effector memory T cells, expression of NK cell receptors (KIR – CD158a/h, CD158bj, CD94, NKG2A, NKG2C) is characteristic [69, 132]. NK receptor expression is controlled by the cytokines IL-2, IL-4, IL-23, TGF-β, IL-15, IL-6, IL-10, IL-21, and also depends on the nature of the antigen (due to the interaction with CD28) [132]. Expression of one of the NK receptors – CD158a/h, is increased in $CD8^+$ T lymphocytes of the decidua compared to $CD8^+$ T lymphocytes of peripheral blood; the expression of the remaining NK receptors on $CD8^+$ T lymphocytes of the decidua and peripheral blood is the same [132]. At the same time, decidual $CD8^+$ T lymphocytes are characterized by reduced cytotoxic activity compared with peripheral $CD8^+$ T lymphocytes. One of the proposed mechanisms for this phenomenon may be the reduced expression of FasL, as well as perforin and granzyme B. At the same time, high expression of mRNA perforin and granzyme B was established, which indicates a post-translational mechanism of blocking the production of these proteins [130, 134]. Also, reduced cytotoxicity may be associated with the effect of the locus molecules HLA-G and HLA-C expressed by the trophoblast. The functions of NK receptors on $CD8^+$ T lymphocytes have not been adequately studied at present.

The decidual $CD8^+$ T lymphocytes of the first trimester of pregnancy secrete *in vitro* CSF2, IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, and TNF (especially IFNγ and IL-8), that stimulates trophoblast invasion [91, 114]. A high level of TGF-β provides a high threshold level of cytolytic activity of $CD8^+$ T lymphocytes in the decidua [21], which also contributes to the successful invasion of trophoblast. This effect can be associated with suppression of CD8 molecule expression by cytotoxic T lymphocytes in the presence of TGF-β [98].

An ICOS molecule is expressed on 96% of decidual $CD8^+$ T lymphocytes [91], which belongs to the family of CD28-B7 costimulatory molecules. Expression of ICOS is inducible. ICOS binds to ICOSL, expressed on professional APC (B cells, macrophages, DC), epithelial and endothelial cells [143], including on the trophoblast [91]. It was noted that as a result of ICOS binding to ligand, decidual $CD8^+$ T lymphocytes secrete more IFNγ and IL-10 than $CD8^+$ T lymphocytes of peripheral blood [91]. Such stimulation of secretory activity of $CD8^+$ T lymphocytes upon contact with trophoblast through ICOS can be directed to stimulation of trophoblast invasion. It was shown that the ICOS molecule is important for the realization of the immunological response by T helper cells (cell proliferation, activation), T regulatory cells (differentiation, proliferation) [146] and Th17 lymphocytes [61, 91, 143]. The important role of the ICOS molecule expressed by $CD8^+$ T lymphocytes in the antigen-dependent response in tissue transplantation has been shown. In particular, in the "graft versus host" system, the deletion of ICOS on $CD8^+$ T lymphocytes leads to a fatal outcome, caused by excessive expansion and secretory activity of $CD8^+$ T lymphocytes [153]. In peripheral $CD8^+$ T lymphocytes, early expression of ICOS results in migration to non-lymphoid organs, increased cytolytic activity and decreased ability of $CD8^+$ T lymphocytes to participate in the development of a secondary immune response [82]. Probably, decidual $CD8^+$ T lymphocytes thus contribute to the formation of a favourable cytokine microenvironment and a decrease in the cytotoxicity of the cells of the immune system of the mother during the trophoblast implantation. On the other hand, decidual $CD8^+$ T lymphocytes of the first trimester of pregnancy *in vitro* have the ability for extracellular cytolysis [114]. When decidual $CD8^+$ T lymphocytes are exposed to proinflammatory cytokines and activation of their TcR, their expression of perforin and granzyme B, as well as their degranulation of cytotoxic granules, is enhanced, which distinguishes these cells from decidual NK cells characterized by greatly reduced cytolytic activity [21]. Simultaneously, decidual $CD8^+$ T lymphocytes produce more granulin as compared to a similar subpopulation of peripheral blood, which can provide local protection against intracellular and extracellular pathogens [21].

The proteins Tim-3 (T cell immunoglobulin mucin-3) and PD-1 (programmed cell death-1)

are important signalling molecules of CD8+ T lymphocytes. Their functions have not been sufficiently studied. The high level of expression of PD-1 and Tim-3 CD8+ T lymphocytes correlates with reduced antiviral activity of these cells, reduced proliferative activity of CD8+ T lymphocytes and reduced secretion of pro-inflammatory cytokines CD8+ T lymphocytes, while their blockade leads to restoration of proliferation and synthetic activity cells [57, 100]. There is also evidence that the interaction of PD-1 and B7-H1 determines the cytotoxic pathway of differentiation of CD8+ T lymphocytes [40]. Signals from PD-1 and Tim-3 synergistically reinforce each other [57, 140]. It has been shown that Tim+PD-1+CD8+ T lymphocytes are concentrated in the decidua in a physiological pregnancy and participate in the establishment of pregnancy in the early stages [57, 140, 149]. Tim+PD-1+CD8+ T lymphocytes show an increased level of proliferative activity in comparison with Tim-3-PD-1-CD8+ lymphocytes, have greater expression of activation markers CD69 and HLA-DR and greater secretion of Th2 cytokines (in particular, IL-4 and IL-10) [140]. In the case of spontaneous abortions, both the amount of Tim+PD-1+CD8+ T lymphocytes in the decidua, and the production of anti-inflammatory cytokines are reduced. At the same time, increased production of proinflammatory cytokines IFNγ and TNFα is observed [149]. The mouse model shows that the blockade of Tim-3 and PD-1 leads to a significant decrease in the weight of the foetus and the number of offspring, which indicates the important role of these molecules in providing foetal protection and normal pregnancy [140]. In women with spontaneous abortions, an association of a decreased number of decidual CD8+ T lymphocytes with the PD-1+CD8+ phenotype and a decreased proliferative activity has been observed [140]. PD-1L is expressed on syncytiotrophoblast cells directly in contact with the parent cells [137], which is one of the mechanisms of formation of immunological tolerance for trophoblast cells. Expression of PD-1L with trophoblast is stimulated by EGF and IFNγ [48]. It is likely that increased production of IFNγ trophoblast in early pregnancy [3, 4] and its autocrine effect may be one of the mechanisms of survival of a semi-allogenic foetus as a result of the interaction of PD-1 on T lymphocytes and PD-1L on the trophoblast. From the first to the second trimester, the expression of PD-1L in the placenta is increased, the regulation of expression is probably carried out depending on oxygenation (insufficient oxygenation in the uteroplacental blood flow zone causes a decrease in expression of PD-1L) [49]. Decreased expression of PD-1L in the decidua is associated with habitual miscarriage [77]. Thus, Tim and PD-1 are important in establishing the tolerogenic nature of CD8+ T lymphocyte differentiation in pregnancy.

Factors secreted by the placenta and decidua, significantly affect the formation of immunological tolerance in pregnancy, in particular, affect the apoptosis of the mother's cells. It was noted that the level of apoptosis of CD3+ T lymphocytes in peripheral blood is higher in pregnancy than in non-pregnant women [25]. At the same time, the level of apoptosis of CD3+CD8+ T lymphocytes at the onset of pregnancy is lower than in non-pregnant women, and the maximum level of apoptosis of this subpopulation of T lymphocytes is observed in the first trimester of pregnancy [25], which can be aimed at ensuring foetal survival in early pregnancy and elimination of alloreactive cells. The decidua produces significant amounts of glycodelins A (GdA), which inhibits the cytotoxic activity of activated CD8+ T lymphocytes and their proliferation [123] using CD7 as a receptor [125]. GdA suppresses the synthesis of IL-2R, which interferes with the action of IL-2 on T lymphocytes and the formation of functionally mature cytotoxic cells [122]. The placenta secrets the preimplantation factor (PIF), which binds to the proteins of the CD8+ T lymphocytes cytoskeleton and suppresses the immune response of the mother [12]. Interaction with soluble HLA-C, whose concentration in the peripheral blood rises in pregnancy, causes apoptosis of CD8+ T lymphocytes by enhancing its production of FasL [19, 104].

CD8+ T lymphocytes active against paternal antigens, including anti-minor histocompatibility antigens (mHag-peptides derived from polymorphic proteins, recognized as heterogenous) have been described in the literature, but they do not exert any influence on the outcome of pregnancy [131]. This may be due to the formation of subpopulations of regulatory CD4 and CD8 lymphocytes, levelling their influence [131].

In pregnancy, virus-specific CD8+ T lymphocytes accumulate in the decidua [134]. But since decidual CD8+ T lymphocytes acquire more regulatory properties than cytotoxic ones, while retaining the ability to recognize the antigen present in the HLA locus molecule, including the viral antigen – there is no complete elimination of the infected cells [21, 134]. Most likely, the activity of CD8+ T lymphocytes can be aimed at resisting a viral infection in the context of maintaining pregnancy.

Thus, decidual CD8+ T lymphocytes differ in phenotype, secretory and cytolytic activity from CD8+ T lymphocytes of peripheral blood, which is aimed at supporting the invasion of trophoblast in the early stages of development of pregnancy, as well as the

formation of immunological tolerance for the half-allogenic foetus. The disturbance of the homeostasis of decidual $CD8^+$ T lymphocytes has serious consequences that affect the outcome of pregnancy. The mechanisms of maintaining the balance of the functioning of $CD8^+$ T lymphocytes within the framework of maintaining the physiological course of pregnancy and at the same time effective protection against infectious agents remain insufficiently studied. The diverse interaction of $CD8^+$ T lymphocytes with microenvironment cells in the utero-placental blood flow zone has a significant effect on the nature of the functional activity of all interacting cell types.

Intercellular interactions of $CD8^+$ T lymphocytes

In pregnancy, trophoblast cells play a central role in the development of immunological tolerance. In the regulation of the cytotoxicity of immune system cells from the trophoblast side, the expression of the locus molecules of the main histocompatibility complex HLA-G and HLA-C is important. Receptors for the molecules of the HLA-G locus on $CD8^+$ T lymphocytes are the molecules CD8, LILRB1 and CD160 [72]. HLA-G locus molecules are expressed on the trophoblast in combination with endoplasmic reticulum aminopeptidase 1 (ERAP1), which generates peptides capable of forming a stable complex with HLA-G [106]. This contributes to the successful invasion of the trophoblast. Expression of this complex on trophoblast cells is enhanced by exposure to LIF and VEGF [106]. The extravillous cytotrophoblast produces both a membrane and a soluble form of HLA-G [59, 67]. The soluble form is found not only in the amniotic fluid, but also in the mother's bloodstream [13, 45, 120]. It was shown that the soluble form of the HLA-G locus molecule promotes immunological tolerance, causing apoptosis of $CD8^+$ T lymphocytes [73], including through interaction with the CD8 molecule [72]. HLA-G locus molecules can also inhibit the proliferation of $CD4^+$ lymphocytes, thereby reducing the risk of developing a mixed lymphocyte response from both the mother and the foetus. The low level of production of HLA-G by the trophoblast is associated with complications, including the development of preeclampsia [45, 85]. At the same time, some of the latest studies have revealed an increased level of HLA-G mRNA in the decidua in preeclampsia [103].

Prostaglandin E2 (PGE2), indolamine 2,3-dioxygenase (IDO) and TGF-β also participate in the suppression of proliferation of $CD8^+$ lymphocytes [80].

According to the latest data described in the literature, several stages can be distinguished in the interaction of trophoblast and $CD8^+$ T lymphocytes. First, direct recognition of HLA-C by the T cell receptor of $CD8^+$ T lymphocytes. Further, a peptide (viral or allogenic) is presented in the MHC I complex, activation of CD8 lymphocytes. The mouse model shows that the presentation of foetal antigens occurs exclusively in an indirect way, due to maternal APC, and antigen presentation occurs only in the late stages of pregnancy, which is associated with the late onset of the expression of MHC I molecules on foetal cells [18, 21, 36]. At the same time, it has been repeatedly shown that macrophages and DC of the placenta and decidua are of a tolerogenic nature [26, 38, 79, 116, 118, 139, 144]. The literature also describes the presentation of minor and major histocompatibility antigens in the maternal APC after the capture of trophoblast debris by $CD4^+$ T lymphocytes, which in turn secrete cytokines that affect the differentiation of $CD8^+$ T lymphocytes.

Antigen-presenting cells and trophoblast produce significant amounts of IL-27 [20, 43, 107]. In naïve $CD8^+$ T cells ($CD8^+CD45RA^+CCR7^+$), IL-27 enhances the expression of the T-bet transcription factor, which indicates the polarization of $CD8^+$ T lymphocytes in the Tc1 direction, stimulates proliferation, IFNγ secretion, granzyme B and cytotoxicity of these cells [117]. However, the mechanisms of influence of IL-27 on the development of pregnancy remain unclear. The IL-27 receptor is expressed on $CD8^+$ T lymphocytes to a greater extent than on $CD4^+$ lymphocytes, mainly on $CD8^+CD45RO^+$ lymphocytes (i.e., memory cells) [117]. Intracellular expression of the IL-27 receptor (TCCR/gp130) is characteristic of naïve cells, with activation the surface expression of the receptor is enhanced [117]. The mouse model shows that the production of IL-27 by the decidua is enhanced before implantation [86]. In women with habitual miscarriages, much lower expression of IL-27 in the decidua is observed compared to women with spontaneous abortion and the physiological course of pregnancy [141].

The extravillous cytotrophoblast expresses the B7H2 molecule (ICOS ligand). The specific interaction of ICOS/B7H2 contributes to the secretion of T cells by cytokines IFNγ, IL-10 and IL-2 [91]. According to other data, foetal formation causes strong proliferation of $CD8^+$ T lymphocytes in the uterine lymph nodes during pregnancy, but they are simultaneously susceptible to clonal deletion [36]. The remaining activated $CD8^+$ T lymphocytes are characterized by reduced secretion of IFNγ, IL-2 and IL-4 and inability to cytolytic activity [36]. Previously, it was also noted that IL-4, secreted by Th2, leads to a decrease in the production of IFNγ, TNFα and IL-10 by Tc1 cells [110].

It has been established that trophoblast stimulates the formation of a subpopulation of $CD8^+$

T regulatory cells [77, 119]. Since activation of $CD8^+$ T lymphocytes involves $CD4^+$ T lymphocytes, they will have a significant effect on the functioning of cytotoxic T lymphocytes. $CD4^+$ Treg cells by secretion of IL-10 contribute to the formation of $CD8^+$ cell memory in viral infection [71]. $CD4^+$ Treg lymphocytes suppress $CD8^+$ T cell response: $CD4^+$ Treg cause apoptosis of $CD8^+$ cytotoxic T lymphocytes and reduce their expression of granzymes A and B [44]. $CD4^+$ Th1 lymphocytes are involved in the induction and maintenance of viability of $CD8^+$ lymphocytes (Tc1), both effector and memory cells, through IL-2 secretion, activation of DC by CD40/CD40L interactions, and also using pMHC I [51]. $CD8^+$ Treg stimulate the differentiation of $CD4^+$ Treg [75]. Subpopulations of CD8 Tc1 and Tc2 lymphocytes differently influence the differentiation of $CD4^+$ T lymphocytes: in the presence of Tc1, Th1-lymphocytes predominate, and in the presence of Tc2, Th2-lymphocytes predominate [138]. It has been shown that $CD8^+$ T lymphocytes stimulate the expansion of cells of a specific subset of $CD4^+$ Treg expressing the TCR Vβ5 chain whose proliferation regulation mechanism differs significantly from other Tregs and does not depend on IL-2 [58]. The enhancement of the surface expression of TNFα, observed with the activation of $CD8^+$ lymphocytes, promotes the expansion of $V\beta5^+$ Treg lymphocytes [58]. Simultaneously, the expression of TNFR2 on $V\beta5^+$ Treg plays a leading role in inducing the proliferation of these cells [58]. The action of Treg is aimed at limiting the cytotoxic activity of $CD8^+$ T lymphocytes, therefore the revealed regulation mechanism is a system of mutual influence of T cell subpopulations during the antiviral response. The results were obtained on a mouse model, but there is reason to assume that such a mechanism exists in humans [58].

The secretory products of decidual $CD8^+$ lymphocytes of the first trimester of pregnancy stimulate trophoblast invasion [114], which can be mediated by the action of IFNγ. Secreted by $CD8^+$ lymphocytes, IL-8 can play an important role in vascular remodelling in the first trimester of pregnancy by stimulating MMP production. Thus, $CD8^+$ lymphocytes contribute to the formation of the placenta in the early stages of pregnancy.

The trophoblast cells (including due to the production of the locus molecules HLA-C and HLA-G), T helper lymphocytes, APC of the placenta and decidua, have a significant effect on the formation of the subpopulation composition of $CD8^+$ T lymphocytes of the decidua. In turn, decidual $CD8^+$ T lymphocytes affect trophoblast cells and $CD4^+$ T lymphocytes; however, the molecular mechanisms of these cell-cell interactions have not been sufficiently studied.

Conclusion

The population of $CD8^+$ T lymphocytes is a collection of cells quite diverse in phenotype and function. Great importance is attributed to subpopulations of memory $CD8^+$ T lymphocytes and $CD8^+$ Treg, identified relatively recently. Differentiation of $CD8^+$ T lymphocytes depends on the cytokine environment and antigen presentation involving surface molecules. Not only differentiation is possible in the primary lymphoid organs, but also in the secondary ones; however, the molecular mechanisms for the regulation of differentiation of $CD8^+$ T lymphocytes have not been adequately studied. Migration of $CD8^+$ T lymphocytes to the decidua is caused both by changes in expression of surface molecules of $CD8^+$ T lymphocytes under the action of soluble products in the utero-placental contact zone, and by changes in the production of soluble and surface molecules by cells of the decidua. Molecular mechanisms of specific migration of $CD8^+$ T lymphocytes in pregnancy are poorly understood. An important role of the concentration of $CD8^+$ T lymphocytes in the endometrium and decidua during the whole pregnancy is distinguished. Violation of the quantitative content or functional activity of $CD8^+$ T lymphocytes in the decidua can lead to serious complications of pregnancy. $CD8^+$ T lymphocytes in the utero-placental contact zone interact with a wide range of cells. Their functioning in these tissues is aimed at stimulating the invasion of trophoblast and the formation of immunological tolerance, accompanied by a decrease in its own cytotoxic activity and an increase in regulatory function. However, the molecular mechanisms of intercellular interactions are subject to further detailed study.

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