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РОЛЬ РАЗЛИЧНЫХ СУБПОПУЛЯЦИЙ CD4+Т-ЛИМФОЦИТОВ ПРИ БЕРЕМЕННОСТИ

Соколов Д.И., Степанова О.И., Сельков С.А.

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

Резюме. Важную роль в формировании иммунологической толерантности при беременности играют Т-лимфоциты. В настоящем обзоре рассматривается характеристика Т-лимфоцитов децидуальной оболочки и плаценты, особенности их миграции и функциональной активности при беременности. В обзоре обсуждается роль субпопуляций Th1-, Th17-, Th2- и Treg-лимфоцитов в формировании плаценты и иммунорегуляции беременности, а также их взаимодействие с клетками децидуальной оболочки и трофобласта.

Ключевые слова: беременность, плацента, лимфоциты, трофобласт, децидуальная оболочка

THE ROLE OF THE DIFFERENT SUBPOPULATIONS OF CD4+T LYMPHOCYTES DURING PREGNANCY

Sokolov D.I., Stepanova O.I., Selkov S.I.

D.O. Ott Research Institute of Obstetrics, Ginecology and Reproductology, St. Petersburg, Russian Federation

Abstract. An important role in the formation of immunological tolerance during pregnancy play T lymphocytes. In the present review discusses the characteristics of T lymphocytes, decidua and placenta, especially their migration and functional activity during pregnancy. The review discusses the role of the subpopulations of Th1, Th17, Th2 and Treg lymphocytes in the formation of the placenta and the immune regulation of pregnancy, as well as their interaction with the cells of the decidua and trophoblast.

Keywords: pregnancy, placenta, lymphocytes, trophoblast, decidua

Introduction

Pregnancy is an example of the unique cooperation between the maternal and the semi-allogenic fetus organism. During pregnancy an adaptation to fetus development and securing of maternal organism, first of all her immune system, occurs. An important aspect of maternal immune response transformation is a formation of immune tolerance, in development of which decidua macrophages [3], T lymphocytes, and NK cells play a significant role. T lymphocytes take an active part in preparing endometrium for blastocyst implantation and forming favorable microenvironment, as well as further development of the placenta, fetal membranes, and fetus, and they maintain fetus vitality [13]. The most distinct changes of immune system population cell composition at pregnancy is observed in the zone of the uteroplacental bed, where endometrium

Адрес для переписки:
Соколов Дмитрий Игоревич
ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им Д.О. Отта»
199034, Россия, Санкт-Петербург, Менделеевская линия, 3.
Тел.: 8 (812) 323-75-45, 328-98-50.
Факс: 8 (812) 323-75-45.
E-mail: falcojugger@yandex.ru

Address for correspondence:
Sokolov Dmitry I.
D.O. Ott Research Institute of Obstetrics, Ginecology and Reproductology
199034, Russian Federation, St. Petersburg, Mendeleevskaya line, 3.
Phone: 7 (812) 323-75-45, 328-98-50.
Fax: 7 (812) 323-75-45.
E-mail: falcojugger@yandex.ru

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leucocytes contact with trophoblast cells. Currently, in addition to well-known T lymphocyte populations Th1 and Th2, the following subpopulations are pointed out: T regulatory (Treg), Th17, follicular T helpers (Tfh), Th9, and Th22. Moreover, T cells, combining secretion of cytokines, which are typical for different subpopulations, are distinguished [139]. A theory of the pivotal role of Th1/Th2 paradigm in formation of immune tolerance with respect to semi-allogenic fetus, which was popular for a long period of time, currently fails to satisfy most of researchers, who actively study reproductive process immunology. Thus, a classical scheme, based on balanced immune response, mostly controlled by Th2 lymphocytes, has been completed now with information about the role of Treg and Th17 subpopulations.

T cell subpopulation: differentiation and plasticity of inter-population transitions

At the moment among $CD4^+$T lymphocytes a lot of subpopulations are distinguished, based on the spectrum of cytokines secreted by them and their expression of certain transcription factors (Figure 1, see Cover, p. 2) [45, 101]. In this review, the functions of four subpopulations (Th1, Th2, Th17 and Treg), are considered. The role of which, according to modern ideas, during physiological pregnancy is leading.

Th1 lymphocyte subpopulation is characterized by secretion of pro-inflammatory cytokines, including IL-2, IL-15, TNFα, IFNγ, and controls cellular immune response realization [89]. Th1 lymphocytes express Tbet transcription factor and receptors CXCR3 [97], CCR6 [106], IL-18R [137] CCR5 [91], and some other (Table 1).

Th2 lymphocyte subpopulation is characterized by secretion of anti-inflammatory cytokines IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and controls humoral immune response realization. Th2 lymphocytes express transcription factor Gata3 and receptors CD294 [54], CCR3, CCR4, CCR8, CRTH2, CD62L, CD30 (Table 1) [106]. At that, it should be specified that cytokine division into pro- and anti-inflammatory is relative, and often the same cytokines occasionally have both pro- and anti-inflammatory activity, depending on a situation, such as IL-6 and IL-4.

Differentiation of certain Th lymphocyte subpopulations is controlled by cytokines, secreted by various microenvironment cells, including antigen-presenting cells (Figure 1). Th1 lymphocytes are differentiated form naive Th0 lymphocytes in the presence of IL-12 (STAT4 signal path), which is accompanied by an increase of T-bet transcription factor expression [101, 114]. IL-33 cytokine, being a transcription factor, secreted by macrophages, dendritic cells (DC), and epithelial cells, in the presence of IL-2 stimulates Th1 differentiation and their IFNγ secretion [50]. It has been determined, that IL-18 combined with IL-12 increases secretion of IFNγ by Th1 cells [137]. TGF-β inhibits IFNγ-mediated differentiation, proliferation, and secretion of cytokines by Th1 cells [40, 86, 121]. Recently, an alternative method of Th1 differentiation, constituting an action of cytokine IL-4, TGF-β, and IFNγ totality on naive T lymphocytes, has been described [126]. Th1 lymphocytes, obtained in such a way, are distinguished by an expression of CD103, thus, the authors do separate them into $CD103^+$Th1 cell subpopulation. The presence of NO or NO and IFNγ combination directs TGF-β-induced naive T cell differentiation in Th1 direction [57]. IL-4, IL-6 [26], transcription repressor Gfi1 [119] participate in inhibition of differentiation in Th1 direction.

TABLE 1. THE CHARACTERISTICS OF $CD4^+$T LYMPHOCYTE SUBPOPULATIONS

T-lymphocyte subpopulation	Marker combinations, used for the identification of a population	Other surface molecules	Secreted cytokines
Th1	CD4, IL-18R [137], CCR5 [91]	CXCR3, CCR6 [106] CD26, membrane form IFNγ, LAG-3, CCR5, CXCR3 [1]	IL-2, IL-15, TNFα, IFNγ
Th2	CD4, CD294 [54]	CCR3, CCR4, CRTH2 [106], CD62L, CD30, CCR8 [1], CD103 [126]	IL-4, IL-5, IL-6, IL-13
Th17	CD4, CCR6, CD161 [7, 23], RORγt [106, 111], CD26 [11]	RORct, IL-23R, IL-12R, [7], CCR2, CXCR3, CCR5, CXCR6, CCR4, CD62L, CCR7, CXCR4, CXCR5 [46]	IL-17A, IL-22, IL-21, IL-17F, IL-26 [87, 89], TNFα, limphotoxin-β [7, 101, 106]
Treg	CD4, CD25, Foxp3, $CD127^{low}$ [56, 66], CTLA-4 (intercellular) [49], $CD4^+CD25^{high}CD62L^{high}$ [10, 56], FoxP3, neiropilin-1 [141]	GATA3, CD28 [122], CD45RO, CD45RB, CD45RA, CD44, integrin α4β7, CTLA-4, CCR9, OX40, CCR7 и CD62L, CCR2, CCR4, CCR5, CCR6, CCR8, CCR9, CCR10, CXCR3, CXCR5, CXCR6	IL-10, TGF-β, IL-4, IL-5

Th2 lymphocyte pool is formed mostly in the presence of IL-4, IL-33 and absence of IL-12 [73, 102]. IL-1 [110], IL-6 [26] also take part in Th2 differentiation. Th2 differentiation is controlled by transcription factors STAT6, GATA3, c-maf [1]. Estradiol and progesterone, an increase of which is observed in peripheral blood during pregnancy, stimulate IL-10 DC secretion, facilitating Th2 differentiation [131]. Progesterone direct action on Th2 differentiation stimulation and Th1 differentiation inhibition [75] has been determined, which may be important for peripheral cell differentiation in view of high progesterone concentration in decidua. Decidua DCs express co-stimulatory molecules CD80, CD86, CD83 and secrete small amounts of IL-12, facilitating Th2 differentiation [76].

Th17 lymphocytes, through cytokine IL-17 secretion, cause secretion by target cells of wide pro-inflammatory cytokine spectrum. Th17 lymphocytes are characterized by expression of molecules RORγt (retinoic acid related orphan receptor γt), IL-23R, CCR4, IL-12R, CD161 and high expression level of chemokine receptor CCR6 (Figure 1, Table 1) [7, 39, 97]. These cells secrete IL-17A, IL-17F, IL-22, IL-26, lymphotoxin-β [7, 101, 106], IL-21 [87, 89]; they produce TNFα in higher amounts than T cells of other populations, by means of which their participation in pathogenic processes is realized [19]. Th17 are involved in protecting the organism from bacteria, fungi and viruses; and participate in the pathogenesis of many autoimmune diseases [101]. It should be mentioned that this subpopulation combines the heterogeneous cell group, among which there are: 1) cells, producing IL-17, IL-22 and expressing CCR6 and RORγt; 2) cells with properties of both Th17 and Th1 lymphocytes, simultaneously producing IL-17 and IFNγ and expressing ROR-γt and T-bet (they serve as a marker of IL-17 and IFNγ functionality, respectively); 3) highly-proliferative cell type, secreting at an early stage of differentiation either IL-17 in conjunction with IL-10, or IL-17 in conjunction with IFNγ [106]. For a short period of time (3-5 days after antigen stimulation) human Th17 produces significant amounts of IL-10, its secretion is stimulated under IL-23 and IL-27 action and inhibits in the presence of IL-1β [106]. Naive T lymphocyte differentiation into Th17 depends on the type of pathogen, penetrated into an organism, and cytokines, secreted by antigen-presenting cell. Thus, it has been determined that DCs with $CD103^{-}CD11b^{+}$ phenotype, producing TNFα, IL-6, IL-12p40 and IL-23p19 after LPS stimulation, induce Th0 differentiation in the direction of Th17 cells. On the contrary, DCs with $CD103^{+}CD11b^{-}$ phenotype produce IL-10 and stimulate naive T lymphocyte differentiation into $FoxP3^{+}$Treg (Figure 1) [46]. According to different data, soluble factors TGF-β, IL-1β, IL-6, IL-21, IL-23, prostaglandin E2 in various combinations [1, 5, 7, 15, 23, 46, 59, 70, 71, 72, 88, 97, 102, 110, 114, 127] take part in Th17 differentiation. Other authors noted that TGF-β had no impact on Th17 differentiation and only weakly suppressed their proliferation [111]. According to different data, the action of TGF-β, combined with IL-1β and IL-6, hampers [101], or *vice versa* facilitates [32, 102] Th17 differentiation. There is some information that small amount of TGF-β promotes Th17 differentiation, while large concentrations *vice versa* inhibit Th17 differentiation [106]. At that, compared to Th1 and Th2 subpopulations, Th17 has lower sensitivity to TGF-β inhibiting action [7]. Inhibiting of Th17 formation occurs in the presence of cytokines IL-2, IL-27, IL-4, and IFNγ [46, 59, 65]. Retinoic acid [20] and growth factor independent 1 (Gfi1) [41], progesterone (using STAT5 and STAT3 signal paths) [55], transcription factor Ets-1 [101] participate in Th17 and inducible Treg differentiation restriction through RORγt receptor. CD200R binding with its ligand CD200 (OX-2) [95] contributes to Th17 differentiation inhibiting, which may underlie effectiveness of lymphocyte vaccination at habitual non-carrying of pregnancy [2].

Currently much attention is paid on Treg lymphocyte subpopulation, as main immunoregulatory cells at pregnancy, which control immune tolerance formation in the mother-fetus system. It is assumed that in the decidua, the Tregs mainly fulfill immunosuppressive action [16]. Treg lymphocytes have anti-inflammatory and immunosuppressive effects [96], secrete IL-10, TGF-β, IL-4, IL-5 [32], express GATA3 (Figure 1, Table 1) [29]. Treg lymphocytes inhibit proliferation and production of cytokines by T cells, production of immunoglobulins by B-cells, cytotoxic activity of NK-cells, DC maturation, and, thus, contribute to tolerance formation [104]. Treg suppresses $CD4^{+}CD25^{-}$ T cell differentiation into Th1, involving intercellular contacts and TGF-β [115].

Treg cells include $CD4^{+}$T lymphocytes, expressing $CD25^{high}$ and able to have suppressive action on autoreactive T lymphocytes [140]. It should be noted that CD25 is not a molecule, necessary to realize Treg suppressive properties [109]. Treg is characterized by low CD127 expression, reduced CD4 ($CD4^{dim}$), $CD45RB^{low/-}$ expression [78], CD28 expression [109], intracellular CTLA-4 (cytotoxic T lymphocyte antigen) expression [32]. CTLA-4 takes part in restriction of Treg proliferative activity, population homeostasis, and execution of their suppressive properties in respect of effector T lymphocytes [49, 109, 122]. CTLA-4 deletion results in T cell activation and systemic autoimmune reaction development [98, 104]. At Treg activation CTLA-4 expression increases [49]. CTLA-4 blocking has an effect on Treg that is similar to TGF-β blocking, and, moreover, it

stimulates superficial TGF-β Treg expression [109]. Maintenance of Treg proliferative activity occurs at CD28 binding with its ligand [109, 122]. Also these cells express FoxP3 transcription factor, required for realization of Treg cell suppressive properties [87].

By the differentiation nature there are Tregs, maturing in the thymus (tTreg or nTreg – naive), and Tregs, maturing at the periphery (pTreg or iTreg –induced). Naive Treg (nTreg) cells with $CD4^+CD25^+FoxP3^+$ phenotype mature in the thymus [87]. nTreg subpopulation also expresses the following markers: CD45RO (memory cells, activated), CD45RB (quiescent cells), $CD45RA^+$, CD25, CD44, integrin α4β7 (quiescent cells), intracellular CTLA-4, CD28, chemokine receptors, CXCR4, CCR9 (quiescent cells), OX40 [87], Helios [32], as well as CCR7 and CD62L receptors, allowing them to migrate into lymphatic nodes [32]. In FoxP3 the structure that exists is conservative non-coding sequence 1 (CNS1), specific for induced Tregs (iTreg) [134]. Among iTreg there are 1 type Tregs (Tr1) and Th3 Tregs. Tr1 lymphocytes secrete IL-10, TGF-β, IL-2, IL-5, IFNγ [8, 85, 87]. These cells have suppressive action through IL-10 secretion [87]. There is no specific marker to mark this subpopulation, however, they are determined by GATA-3 (ROG) expression [87]. Suppressive action of this Treg subpopulation is less dependent from FoxP3 expression [10]. Treg Th3 subpopulation is characterized by TGF-β and IL-10 secretion and FoxP3 expression [87].

$CD4^+CD25^-$ alteration into Treg cells at the periphery (outside the thymus) occurs with obligatory B7 molecule co-stimulation [61], at activation through TcR [35] in cooperation with action of IL-10 and TGF-β cytokines [42, 109, 121], the source of which is the trophoblast in the zone of the uteroplacental bed [17, 29, 96, 120]. Estradiol promotes Treg differentiation and increases their proliferation in response to activation through CD3/CD28 [131]. There is also information about the necessity of IL-2 for Treg differentiation from cells with $CD4^+CD25^-$ phenotype [87, 131]. Participation of TRAIL molecule in stimulation of T cell differentiation into Treg cell population was also noted [120]. Main growth factor for Treg1 is IL-15 [87]. Furthermore, Treg1 cell (with $FoxP3^-$ phenotype, producing IL-10) differentiation takes place with IL-27 and TGF-β action [9]. Treg Th3 is differentiated under TGF-β action form naive $CD4^+$T cells [87]. Thymic stromal lymphopoietin (TSLP – cytokine from IL-7 family), secreted by the trophoblast, stimulates Treg differentiation with suppressive properties and high level of TGF-β1 and IL-10 secretion from $CD4^+CD25^-$T cells, however, this process requires TGF–β presence [29]. To realize the TGF-β-induced FoxP3 expression stimulation, accompanying peripheral Treg differentiation, the CNS1 sequence is required [107]. CNS1 deletion causes both Treg level reduction (and as a consequence, increased risk of spontaneous abortions), and coiled artery dyspoiesis and reduction of placenta vessel thickness that morphologically corresponds to pathologic inflammation [107]. Progesterone stimulates $CD4^+$ naive cell differentiation from the bone marrow into Tregs, predominantly the memory cells (with $CD45RA^-CD45RO^+$ phenotype) [55]. Naive Treg cells are distinguished by $CD45RA^+$ $CD45RO^-CD31^+$ phenotype, and memory cells by $CD45RA^-CD45RO^+CD31^-$ phenotype [32]. While activating Tregs obtain CD45RO phenotype [32], the suppression of T lymphocyte differentiation in Treg direction takes place with IL-6 [55], NO and IFNγ participation [57].

In the mouse model it has been demonstrated that Th1-population activation can block differentiation of Tregs, specific for fetus antigens, and can promote spontaneous abortion development [136]. T cell differentiation occurs with close interaction with DC. In the beginning of pregnancy the DC concentration in endometrium is higher compared to non-pregnant women, or women at terminal pregnancy stages [51], at that, a lot of immature DCs are observed [44, 51]. Immature maternal DCs through reduced activity of ICAM-1/LFA-1 interaction, IDO (indoleamine 2,3-dioxygenase) expression, and IL-10 secretion, contribute to peripheral Treg development [109, 131]. Also, immature DCs promote Th2 cytokine secretion [131]. IDO molecule, besides stimulation of Treg differentiation, plays also an important role in DC auto-regulation, increasing their secretion of IL-10 and TGF-β [131], as well as in suppression of NK-cell cytotoxic activity.

HLA-DR is a parameter for Treg division into subpopulations with various mechanisms of suppressive action and, probably, reflects Treg maturity degree. A group of terminally differentiated effector cells, expressing HLA-DR, has rapid suppressive effect exclusively through contact interaction of CD39 and ICOS (inducible T cell co-stimulator) molecules. This molecule expression reflects an intensity of suppressive cell activity. HLA-DR negative cells demonstrate a delayed suppressive effect through contact interaction and secretion of IL-4 and IL-10 [10].

For $CD4^+$ lymphocytes a certain plasticity of interpopulation transfers of T cells was described. Th1 and Th2 populations are considered to be quite stable, while in Th17 and Treg populations high instability and plasticity is observed. IL-2 can both stimulate Th1 differentiation and suppress Th17 and Treg differentiation, and alter already differentiated iTreg profile, thus, changing lineage, established with TGF-β [91]. It is believed that Treg and Th17 originate from common progenitor, and TGF-β concentration defines T cell lineage: its low

concentrations play an important role in autocrine maintenance of Th17 population differentiation, while TGF-β high concentrations facilitate progenitor-cell differentiation into Treg (Figure 1) [101]. A possibility to differentiate Th17 into Th1 under IL-12, IL-23 action was demonstrated [7, 89, 102, 106]. It has been determined that naive Th0-cells with IL-1β and IL-23 are differentiated into Th17; IL-12 introduction into this system directs Th0 differentiation into Th1 [23]. A possibility of Treg transformation into Th17 with IL-1β and IL-2 was noted. In the mouse model the Treg cell differentiation into Th2 and Th1 was shown [32]. Th1 can differentiate into Th17 with cytokine IL-1β/IL-6/IL-23, TGF-β/IL-6, or TGF-β/IL-6/IL-23 combinations; Th17 transfer to Th1 with IL-12/IL-23, TGF-β/IL-6 [64]. With interaction through surface molecule B7-H1 Th1 differentiation into Treg is carried out [6]. In the presence of IL-4 Th17-lymphocyte a differentiation shift in the direction of Th17/Th2 subpopulation, secreting IL-17A and IL-4 (Th17/Th2), as well as IL-5, IL-13, IL-21 and IL-22, and promoting IgE secretion *in vitro*, is observed [68]. In the *in vitro* conditions a possibility of Th2 reprogramming with IFNα, IFNβ, and IL-12 into a hybrid of Th1 and Th2 cells (GATA-3$^+$T-bet$^+$), producing both Th2-cytokines and IFNγ, was demonstrated [37]. The population of cells, simultaneously producing IL-17 and IL-4, can be formed by the stimulation of the Th17 subpopulation, containing CCR6$^+$CD161$^+$ cells, in the presence of IL-4 [58]. And combined action of IFNγ and IL-12 cytokines induces Th17 cell differentiation into Th1/Th17 cell subpopulation [58].

Thus, the main differentiation paths of Th lymphocytes with antigen-presenting cells are now well defined. Alternative differentiation paths are also established, as well as possibilities of interpopulation Th lymphocyte transfers, controlled by cytokines and microenvironment cells. The presence of Th lymphocytes and antigen-presenting cells in the zone of the uteroplacental bed [3], a unique microenvironment, and the presence of most cytokines, participating in Th lymphocyte differentiation control, in this zone, and the presence of lymph vessels in the endometrium and uterine lymph nodes may show evidence of a certain effect of placenta and decidua cells on Th lymphocyte differentiation path at pregnancy.

Localization of T lymphocyte subpopulations at pregnancy

It has been shown in the mouse model that during pregnancy the spleen T and B cells actively proliferate, and an activeness of their apoptosis does not increase [84], which can indicate lack of immunity suppression during pregnancy. In the endometrium of women at early stages of pregnancy a lower T cell count is found compared to non-pregnant women [129]. T cells make up 10-20% of leucocytes *in decidua* [82, 89]. 25-45% of them are CD4$^+$T lymphocytes, and 45-75% are CD8$^+$T cells [82, 89, 132, 133]. T lymphocyte pool in the first trimester constitutes 10% of total decidua lymphocyte count, and 17% in the second trimester of pregnancy [51]. Pregnancy development is accompanied by increase of CD4$^+$T lymphocyte amount in decidua [51, 89]. It has been shown in mouse models that the main pool of T cells is situated inside vessels, and the question about their functional activity in the decidua remain undetermined [82].

Literature data about T cell subpopulation content alteration in peripheral blood, as well as placenta and decidua, depending on pregnancy term are contradictory [48]. Th1-lymphocyte domination in the proliferative phase of the menstrual cycle was established [103]. In the first trimester Th1 (CCR4$^-$CXCR3$^+$CCR6$^-$ phenotype) make up 5-30% of decidua cells, Th2 – 2% [89]. According to some authors' data, Th1 and Th2 cell count in peripheral blood has no changes during the whole pregnancy, and has no variations from their count in the group of non-pregnant women [62, 103]. It has also been noted that in the first trimester of pregnancy Th1 (with CCR6$^-$ phenotype) content in the decidua is higher compared to their content in peripheral blood [77, 103], and *vice versa*, Th1 with CCR6$^+$ phenotype content is higher in blood than in the decidua. Th2-lymphocyte content in the decidua is increased in the first trimester of pregnancy [103], however, other researchers do not confirm this data and evidence that Th2 count in peripheral blood and decidua has no difference [77].

Concerning Th17 cell count in the decidua and peripheral blood during pregnancy, there are also no concurrent views. According to some data, the Th17 cell count in pregnant women's peripheral blood increased compared to non-pregnant women, and was maximal at the first trimester, reducing in the second and third trimesters. At that, the Th17 cell pool did not exceed 1-2% of the total peripheral blood mononuclear cell count [62, 135]. Other researchers found no difference [81] or noted Th17 cell count reduction by pregnancy termination [101]. In the endometrium the Th17 cell count increases with the beginning of pregnancy [81, 101, 135]. In the first pregnancy trimester the Th17 pool constitutes 2% of decidual CD4$^+$T cells [89]. The data on relative Th17 cell count in the decidua are conflicting: according to some information Th17 count in the decidua exceeds the one in peripheral blood [81, 101, 135], in line with other authors' data, Th17 count in blood was higher than in the decidua [77].

For Treg-lymphocyte phenotyping, multiple nonstandard monoclonal antibody kits against both surface markers and transcription factors are used, which can be the reason of a big difference in the results

of various researcher teams. It has been established that Tregs are located in the maternal part of placenta and are not found in fetal membranes [124]. The Treg pool is 5% of decidual $CD4^+$T cells [82] though 14% of decidual $CD4^+$T cells [38, 78, 85, 89, 104]. Treg subpopulation, according to different data, constitutes 2.5 [10] to 8% of blood $CD4^+$T cells and up to 13-20% decidual $CD4^+$T cells [35, 51, 112, 131]. Data on Treg count changes in the dynamics of the gestation course. Many authors showed that at pregnancy Treg ($CD4^+CD25^+$) count increased both in circulation [118], achieving its peak in the second trimester [52, 56, 112, 131], and in zone of uteroplacental contact [87, 96, 108, 125, 143]. In the mouse model it has been found that Tregs increase in lymph nodes at pregnancy [142]. According to other data, the Treg count in circulation has no alterations in pregnant women during the whole pregnancy compared to non-pregnant women [32]. According to some data the Treg count in the decidua has no changes from the first to the second trimester [51]. There is also information about Treg count reduction in circulation in pregnant women at the second trimester compared to non-pregnant women [78]. Such significant discrepancy of results may be caused by different cell phenotyping strategies.

In the mouse model it has been shown that Treg actively proliferate at the beginning of pregnancy and their count increases 10 times compared to non-pregnant animals, which is accompanied by CD44 expression increase [99]. Treg count growth is carried out through both $FoxP3^-$ cell differentiation into $FoxP3^+$ cells, and existing $FoxP3^+$Treg proliferation [99]. A similar mechanism can be realized in pregnant women organisms. In Treg pool formation at pregnancy seminal antigen stimulation, noted already at early stages of pregnancy, plays an important role [52, 99]. By the time fertile age begins, thymus activity is reduced, and it is also suppressed by steroid hormones at pregnancy. Thus, Treg expansion during pregnancy is most likely connected with the maturing of these cells at the periphery [87]. At the same time, there is enough data in favor of active thymus participation in Treg maturing during pregnancy, along with the presence of thymus involution morphological changes [52]. At the consecutive pregnancy, Treg accumulation occurs faster than at the first, simultaneously, IFNγ $CD4^+$ secretion by the cells is reduced, which indicates an existence of a functionally active memory Treg pool [99].

Thus, despite an inconsistency of data on various $CD4^+$T lymphocyte subpopulation content in endometrium and decidua, their presence in the zone of the uteroplacental bed is incontestable, which, in turn, suggests an existence of definite control mechanisms of their selective migration into the decidua.

T lymphocyte migration in zone of uteroplacental bed

In the third trimester of pregnancy T lymphocyte activation, shown in their increased expression of CD11a and CD49d adhesion molecules compared to T lymphocytes of non-pregnant women [69], is noted, which can promote T cell accumulation in the endometrium and decidua.

Before the beginning of pregnancy Th1 and cytotoxic T cell migration occurs, and in the beginning of pregnancy they remain in the decidua. Th1 are characterized by expression of receptors CCR5 and CXCR3 [105], CXCR4 [4]. It has been shown in the mouse model that with myometrium stromal cell differentiation into decidual stromal cells, their expression of genes, coding chemoattractants for Th1 cells, in particular, CXCL9, CXCL10, CXLC11 and CCL5, is disturbed [83]. It is thought that in this way Th1 cell population can avoid migration into the decidua, thus providing for favorable conditions for pregnancy development. Both excessive and insufficient Th1 activity results in implantation disorders. At that, a link, regulating Th1-dependent T cell response activity, probably is Treg cells, as mentioned before.

Th2 lymphocytes express CCR4, CCR8, and CRTh2, providing for homing of these cells [105, 128]. Active Th2-lymphocyte migration into the decidua is secured by trophoblast production and CCL17 stromal cells (CCR4 ligand) in the first trimester of pregnancy [32].

During pregnancy Th17-lymphocyte accumulation in the decidua is observed. Th1 migration is stimulated by decidual stromal cell secretory products, while trophoblast secretory products have no effect on the migration of these cells [135]. It is believed that this effect is caused by cytokine CCL2 action [135]. It has been shown in various models that Th17 migration is carried out with participation of CCR6, a receptor for CCL20 [39, 75, 92, 138]. Thus, in the inflammatory conditions, CCL20 produced by macrophages, stimulates Th17 migration [60].

Treg lymphocytes migrate into uterus lymph nodes before the implantation and proliferate there [77, 102]. It is thought that there is a control mechanism of Treg selective migration from peripheral blood into the uterus lymph nodes and decidua at the beginning of pregnancy through particular chemokine production by microenvironment cells. Thus, Treg selective migration into the uterus is facilitated by L-selectin expression by microenvironment cells and their secretion of chemokines CX3CL1, CCL2, CCL3, CCL4, CCL5, CCL22, CCL17, CCL20, which interact with the respective receptors of Treg: CD62L, CCR2, CCR4, CCR5, CCR6, CCR8,

CCR9, CCR10, CXCR3, CXCR5, CXCR6 [32, 52, 77, 102, 131]. Gonadotropin (hCG), secreted by trophoblast [52, 53, 102, 140], estrogen, and progesterone [52] also participate in Treg selective migration control.

Thus, the control mechanisms of Th lymphocyte migration into the uterus endometrium and decidua during pregnancy are currently described. It should be noted that widely different Th lymphocyte subpopulations are present in the decidua, which is probably required for induction and maintenance of immune tolerance in the mother-fetus system. Also, the presence of professional antigen-presenting cells, decidual macrophages and DCs, is described in the decidua. However, the question about a mechanism of one or another Th lymphocyte population accumulation in the decidua remains open. Is it a result of selective migration from peripheral blood, or an outcome of in situ differentiation with antigen-presenting cells and a unique cytokine and cell microenvironment?

Phenotypic and functional peculiarities of CD4+T lymphocytes at pregnancy

Significant part of researches in the sphere of T cell response at pregnancy was conducted in mouse models. It should be noted that Th1 and Th2-lymphocyte development in mouse and human is quite similar, while in respect of Th17 and Treg, their different phenotypic characteristics and differentiation and proliferation conditions are noted [114]. Thus, T cell immunity study in mouse models is important, however, it often requires checking in human cells, especially concerning Th17 and Treg.

Placenta and decidua T cells differ by their phenotype from circulating T cells. To realize and maintain pregnancy the decidua T cells secrete increased amounts of IL-4, IL-10, LIF and M-CSF, while peripheral blood cells have no alterations in their secretion profile [89]. This microenvironment effect can be mediated by progesterone action [89]. It has been considered for a long time that Th1 cytokines have negative effect on pregnancy development, however, now this opinion is not believed to be unambiguous. Proinflammatory cytokines IL-11, IL-12, IL-13, IL-15, IL-16, IL-18 to a large degree expressed normally in the zone of blastocyst implantation in the decidua at early stages of pregnancy [14]. There are researches, indicating that exogenous IL-12 introduction have no detrimental action on pregnancy development, mother's, or fetus's condition at early stages [94]. Th2 cytokines IL-4 and IL-10 are necessary for the successful pregnancy in humans [25, 130]. IL-10 cytokine, besides stimulating Th2 cytokine secretion, promotes angiogenesis in placenta, increases trophoblast vitality [12]. According to different data, peripheral blood mononuclears secrete a lot of IL-4 at pregnancy compared to non-pregnant women [107]. According to other data, the beginning of pregnancy is not followed by increased secretion of IL-4 by T lymphocytes [100].

The great majority of decidua T cells are activated by fetus antigens and have $CD45RA^-$ or $CD45RO^+$ phenotype [89]. Fetus immune protection is fulfilled through increased expression of B7-2 and/or CD28 by decidua T lymphocytes and reduced expression of CTLA-4 [44]. At early stages of pregnancy, there is no receptor for IL-2 (CD25) on endometrium T cells in women [13]. On decidua and peripheral T lymphocytes at pregnancy, a reduced expression of ζ-chain CD3 molecule and TcR/CD3-zeta chain is already found at day 14 after implantation [13, 31]. Identified dose-dependent reduction of TcR/CD3-zeta expression by T lymphocytes with blood serum of pregnant women and, to an even greater degree, in amniotic fluid [31, 123], may indicate action of placenta immunoregulatory factors that change this molecule expression. As CD3-zeta activation on lymphocytes promotes Th1-cytokine secretion, suppressing this molecule expression may contribute to immune tolerance formation. We failed to find literature data, indicating a specific alteration of Th1 and Th2 subpopulation phenotype or functions, connected with their presence in placenta or decidua.

Decidua Th17 cells have $\alpha\beta TCR^+CD45RO^+$ $CCR7^-CD161^+$ phenotype, while peripheral blood Th17 cells mostly do not express CD161 [135]. Also, Th17 identification can be carried out by $CCR2^+CCR5^-$ phenotype [113]. Increased Th17-cell count in decidua is noted in women with spontaneous abortions [67]. IL-17 participation in inflammation initiation during premature delivery was noted [43]. Th17 cell participation in infertility formation was observed, as well [56]. On the other hand, Th17 through active TNFα secretion promote Treg activation [19]. In the implantation zone and decidua, increased concentration of unique population of Th17/Th2-lymphocytes (normally quite small in human) compared to peripheral blood was noted [68]. These cells facilitate successful pregnancy development, while their lack results in implantation disorder [68].

In women with recurrent spontaneous abortions, an increased Th1 and Th17 lymphocyte levels and reduced Th2 content in peripheral blood were found [62, 68]. Probably, imbalance between Treg and Th17 can contribute to pregnancy loss or its severe gestational disorders. A lot of pregnancy pathologies, connected with immune tolerance disturbance, are accompanied by Treg dysfunction [29]. In accordance with modern ideas, Treg plays a dominate role in immune tolerance maintenance with respect to the semi-allogenic fetus [52, 107]. The most important is Treg cell presence in decidua during implantation at early stages of pregnancy, while in the middle and at the end of pregnancy Treg neutralization does not

result in pathology [116]. Peripherally differentiated Tregs (iTreg) are specific to paternal antigens, suppress IFNγ and IL-4 secretion by T cells [52, 142], have increased expression of Helios molecule [99]. Also, Tregs inhibit IL-2 production by lymphocytes, thus, reducing Th1 cytokine secretion [35].

Phenotype and functional activity of decidual Tregs differs from those of circulating Tregs. Decidual Tregs express CTLA-4, HLA-DR, CD69, and CD25, more intensively than peripheral $CD4^+CD25^{bright}$ Treg cells, as well as demonstrate higher suppressive activity compared to peripheral blood Tregs [38, 124]. At pregnancy peripheral blood Tregs are noted to have reduced FoxP3 expression, increased CD45RO expression (effector/memory cell marker), and reduced CD45RA expression (naive cell marker), which reflects higher degree of activation of these cells compared to Tregs in non-pregnant women [78]. These alterations may be induced by action of hormones, in particular, progesterone and estradiol [78].

nTreg cell subpopulation can have suppressive action on the following types of cells: $CD4^+$T cells, DCs, $CD8^+$T cells, NKT cells, NK cells, monocytes/macrophages, B cells, mast cells, basophils, eosinophils, osteoblasts [87, 112]. Treg lymphocytes have suppressive action on T cells and/or DCs because of the secretion of soluble factors, intercellular contacts, and competition for growth factors. Soluble factors include production of IL-10, PD-1, TGF-β, LIF, FLG-2 (fibrinogen-like protein-2) [19, 53], granzyme-A, granzyme-B and perforin (causes effector T cell apoptosis), adenosine (blocks effector T cell cycle and hampers DC maturing) [52]. Intercellular contacts include binding of galectin-1 (blocks cell cycle of effector T cells and DCs), CTLA-4 (reduces activity of antigen presentation on DC [96]), induction of IDO into DC or macrophages, which prevents T cell and NK cell activation; the binding of CD223 Treg cells with MHCII on DCs hampers their maturation and antigen presentation; the binding of neuropilin-1 reduces activity of antigen presentation. Tregs have suppressive action through the presence of TGF-β on their surface in bound state [17, 18, 80]. Also Tregs can serve as a trap for IL-2, creating its deficiency for other cells [87]. In the first trimester of pregnancy decidua Tregs stimulate trophoblast cell invasiveness, mediated by IL-10 action (at that, TGF-β secretion by Treg cells limits trophoblast invasion), as well as stimulate HLA-G expression by trophoblast, which promotes reduction of NK cell cytotoxicity [29]. Other authors point out that IL-10 has no effect on implantation and course of pregnancy [130]. It has been established that Tregs inhibit Th1 and Th2 cell activation through IL-10 and TGF-β secretion, as well as through contact interaction owing to CD223 molecules, neuropilin-1, and CTLA-4 [19]. Tregs suppress proliferation of both Th1 and Th2 lymphocytes, however, through high expression of receptors for IL-4 and IL-9 and autocrine nature of these growth factor action, Th2 lymphocytes are less exposed to inhibiting Treg action [24]. It has also been found that Tregs stimulate Th17 differentiation form naive T cells [19].

It has been demonstrated in the mouse model that Treg introduction cancels the risk of abortion, but, with that, it has no effect on Th1 secretion of cytokines (IFNγ and TNFα), and only slightly increases Th2 production of cytokines (IL-4, IL-10) by decidua lymphocytes [141], but then it significantly stimulates TGF-β and LIF production by decidua and trophoblast cells [141].

Thus, Tregs form microenvironment in zone of uteroplacental bed, promoting immune tolerance formation with respect to the fetus. Currently, a theory of balanced interaction of various Th subpopulations, among which the best-understood are Th1, Th2, Th17, and Treg, in the zone of the uteroplacental bed and regional lymph nodes is prevalent. Active interaction of these subpopulations may underlie a multilevel control of immune tolerance maintenance in the mother-fetus system, which is based on duplication of functions and multiple direct and reverse relations. A relatively new mechanism of immune tolerance formation through reciprocal transplacental migration of Tregs and their colonization of lymph nodes, which was named maternal-fetal microchimerism, should be taken into account [27, 30, 47]. It also should be noted that localized in the decidua and regional lymph nodes the immune system cells are also under active effect of trophoblast and decidua stroma cells.

Impact of placenta and decidua cells on T lymphocyte functional state

Decidua cells secrete molecules, regulating subpopulation content and functional activity of T lymphocytes. For example, galectin-1 is a protein of the endogenic glycan-binding protein family, an expression of which by myometrium and decidua cells is selectively increased with Treg [52], as well as with progesterone [143]. Galectin-1 induces effector T cell apoptosis [143]. Reduced galectin-1 expression may underlie Th1 and Th17 activation [140]. Glycodelin A (GdA) is abundantly expressed by decidua stroma and is bound with almost all T lymphocytes. Glycodelin A causes peripheral blood Th1 cell death, increasing expression of Fas and caspase 3- and 9- by Th1 cell subpopulation, having no such effect on Th2 cell subpopulation [54], which contributes to Th2 domination in the decidua at pregnancy.

At pregnancy production of pregnancy zone protein (PZP) and placental protein-14 (PP14) is significantly increased. PZP is found in blood serum, the zone of the uteroplacental bed, amniotic sac, macrophages, and syncytiotrophoblast cells. PP14 protein is discovered in the endometrium, decidua,

blood serum and amniotic fluid [117]. PZP and PP14 synergically increase T cell immunosuppression, displayed in reduction of T cell proliferative activity and reduction of IL-2 secretion by activated T cells. They have no effect on IL-4 secretion by activated T cells. Thus, they can promote Th1 proliferation inhibiting at pregnancy against the background of no negative effect on Th2 cell clonal proliferation [74, 117]. PZP is a protease inhibitor of wide specify, it effects lymphocyte migration, their cytotoxic activity and secretory specifics. PP14 shows immunosuppressive activity as well, it inhibits IL-2 and IL-1β secretion by immune system cells, T cell blast-transformation and can induce T cell apoptosis [117].

Vasoactive intestinal peptide (VIP), which secretion peak in the zone of the uteroplacental bed occurs during early placentation period, increases Treg concentration in the decidua, stimulates LIF secretion by the trophoblast [34], and facilitates maintenance of tolerogenic phenotype of decidua macrophages [140]. VIP also reduces secretion of IL-6, MCP-1 and stimulates secretion of IL-10 by peripheral blood mononuclears in pregnant women [34], which can promote tolerance formation in the mother-fetus system.

Decidua stromal cells represent the source of CCL2, which promotes accumulation of Th2 cell subpopulation in the decidua [36]. It has been found that trophoblast secretory products reduce expression of STAT4 (specific for Th1 cells) transcription factors in T cells and stimulate expression of GATA3 and STAT6 (specific for Th2 cells) [63]. Secretory products of placenta, isolated cells of cytotrophoblast and syncytiotrophoblast stimulate $CD4^+$ cell differentiation into Treg cells with phenotype $CD127^{low}$, CTLA-4^{high}, $CD39^{high}$, CD45R0 [120]. During activation these cells secrete lower amount of cytokines than control cells, and show increased secretion of IL-10, which corresponds to decidua Treg characteristics at early stages of pregnancy [120].

The mechanisms of T lymphocyte proliferative activity suppression from trophoblast [21, 28] include trophoblast capacity to inhibit T lymphocyte secretion of IFNγ, TNF-α, IL-2, IL-4, and IL-1, IL-17 [21, 63], and stimulate IL-5 secretion by activated T cells [21]. According to other researchers' information, trophoblast has the capacity to effect T lymphocyte secretion of IL-4 and IL-10 [63]. Trophoblast production of IDO and expression of HLA-G [48] can also reduce proliferative potential of T lymphocytes.

Among wide spectrum of extracellular proteins, produced by trophoblast and having inhibiting action on T lymphocytes, estradiol, progesterone, hCG, α-fetoprotein, HCS (human chorionic somatotropin, or human placental lactogen HPL), pregnancy-specific-beta1-glycoprotein (SP1), TGF-β2, MIF, thrombospondin-1, and some other, having immunoregulatory properties [28], may be pointed out.

Pregnancy specific glycoprotein 1a (PSG1a), produced by syncytiotrophoblast, can macrophage-mediately inhibit T lymphocyte proliferation and promote Th2 cytokine secretion [79]. It has been determined that trophoblast expresses receptors for IL-17. It has been shown that IL-17, secreted by Th17 cells, promotes proliferation and invasion of human trophoblast and trophoblast cell culture [90], stimulates trophoblast secretion of progesterone [101, 102], dose-dependently stimulates human trophoblast cell migration, and counteracts trophoblast cell apoptosis [135]. However, with excessive Th17 the cells cause fetus rejection [102].

The trophoblast contributes to the tolerance formation with respect to the fetus, among other due to stimulation of Treg differentiation [29]. One of the mechanisms of its realization is trophoblast IDO expression that promotes Treg differentiation [131]. Thymic stromal lymphopoietin (TSLP), secreted by the trophoblast, increases expression of molecules CD40, CD83, CD80, CD86, HLA-DR, Ox-40L on decidual DCs, and stimulates their secretion of IL-10 and TGF-β [29], thus promoting formation of DC tolerogenic phenotype in zone of uteroplacental bed. RANTES, secreted by trophoblast and T cells, can be one of the mechanisms of tolerance formation, being, during the first trimester, a positive regulator of implantation through induction of pro-inflammatory cytokine secretion in moderate amounts, and, on the other hand, causing effector T cell apoptosis and promoting Treg differentiation [33, 140]. Recent researches indicate that sHLA-G5, secreted by trophoblast, promotes formation of Th17/Th2 cell pool in the decidua and reduces the amount of Th17/Th1 or Th17/Th0 clones [68]. Trophoblast cells are the source of hemoxygenase-1 (HO-1), which significantly contributes to physiological pregnancy establishment and immune tolerance formation. Hemoxygenase-1 also shows antiapoptotic action on decidua and placenta cells, it is required for maintenance of trophoblast stem cell vitality and their differentiation. HO-1 stimulation results in the increase of the Treg pool in the decidua and placenta, and Tregs, in turn, stimulate HO-1 expression by trophoblast cells [53].

Thus, decidua and placenta cells secrete a wide spectrum of molecules, controlling vital functions of individual Th lymphocyte subpopulations, their migration into the decidua, alteration in proportion of subpopulation T cell content, their proliferation and functional activity [63].

Conclusion

In spite of a significantly increased volume of information about subpopulation content

of $CD4^+$Th lymphocytes, peculiarities of their differentiation, migration and localization, the question about role of specific subpopulations in immune tolerance induction and maintenance in the mother-fetus system remains open. In the last ten years, a correction of ideas about the role of Th1\Th2 lymphocytes and cytokines, secreted by them, in physiological pregnancy maintenance took place, a lot of information about the role of other Th lymphocyte subpopulations in maintenance of pregnancy occurred. Besides Th1 and Th2 participation, the role of Th17 and Treg in maintenance of physiological gestation course, supplementing the known paradigm Th1\Th2, is the best described. At the same time, it should be admitted that the description of versatile relationships of Th lymphocyte subpopulations with each other and microenvironment cells, capable of changing Th lymphocyte behavior up to correcting their differentiation path, seems to be quite close to *in vivo* situation. It is connected with rapidly changing situations, especially at early stages of pregnancy, when dynamics of relationships between various cell populations alters within a day or even hours. Previously described decidualization of endometrium at pregnancy, rapid change of quantitative and qualitative leukocyte content in the endometrium and decidua, increase of lymphangiogenesis in the endometrium, localization in the decidua of NK cells, various T lymphocyte subpopulations, professional antigen-presenting cells – DCs, macrophages [22, 93] and their possible migration into regional lymph nodes, specific cytokine and cell microenvironment together indicates a possible commitment of naive T lymphocyte differentiation in direction of Treg or Th2 directly in the decidua. Literature analysis indicates that the main direction of immune system cell activity in zone of uteroplacental bed is connected not so much with effector functions, as with immunoregulatory ones. Among effector functions, cytotoxic reactions, controlling trophoblast proliferation and invasion, as well as inducting processes of cytotoxic cell apoptosis, play a significant role. It is very similar to the immune structure of skin and mucous membranes. At the same time, lack of morphologic structures, combining immunocompetent cells in the zone of the uteroplacental bed by the type of lymphoid follicles (or other formations like Peyer's patches in the intestine) in connection with lack of necessity to activate antibody response, makes them more mobile in functional and phenotype transformations, required, first of all, for their realization of regulatory mechanisms.

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Авторы:

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

Степанова О.И. *— к.б.н., старший научный сотрудник лаборатории межклеточных взаимодействий, отдел иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им Д.О. Отта» Санкт-Петербург, Россия*

Селькov С.А. *— д.м.н., профессор, руководитель отдела иммунологии и межклеточных взаимодействий ФГБНУ «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им Д.О. Отта» Санкт-Петербург, Россия*

Authors:

Sokolov D.I.*, PhD, MD (Biology), Head, Cell Interactions Laboratory, Department of Immunology and Cell Interactions, D.O. Ott Research Institute of Obstetrics, Ginecology and Reproductology, St. Petersburg, Russian Federation*

Stepanova O.I.*, PhD (Biology), Senior Research Associate, Cell Interactions Laboratory, Department of Immunology and Cell Interactions, D.O. Ott Research Institute of Obstetrics, Ginecology and Reproductology, St. Petersburg, Russian Federation*

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

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