



The Regulation and Function of T Lymphocyte in Fetomaternal Immunity Tolerance

Lin Y^{1,2,3#}, Zhang D^{1,2,3} and Du M^{1,2,3*}

¹Department of Obstetrics and Gynecology, Fudan University Shanghai Medical College, Shanghai 200011, China

²Department of Reproduction and Development, Fudan University, Shanghai 200032, China

³Department of Female Reproductive Endocrinology, Shanghai 200011, China

[#]Yikong Lin and Di Zhang contribute equally to this manuscript

Abstract

During pregnancy, maternal immune system orchestrates the optimal immune modulation to prevent a detrimental response to allogeneic fetal cells while providing immune protection against pathogen invasion. Accumulating evidences and speculations from recent works lead to the view that decidual T cell subsets play crucial roles in both physiological and pathological processes associated with pregnancy. However, the exact characteristics and functions of these T cell subtypes are undefined. Effector T cells are divided into multiple subsets characterized by the presence of specific transcription factor and cytokine production. Some subsets of T cells are thought to protect the placenta from immune rejection and facilitate embryo implantation, while others are considered to be the main culprits for some pathological pregnancies. It is incontrovertible that not a single cell or molecule but rather a network of communication and interaction should be responsible for the successful pregnancy outcome. The antagonism and cooperation among different T cell subsets are beneficial to create a micro-environment toward maternal-fetal tolerance. Disturbance of the micro-environment may lead to pregnancy complications, including spontaneous abortion, preeclampsia, intrauterine growth restriction, preterm birth and congenital infection. This review is focused on different T cells and their interaction with immune-regulatory molecules and endocrine factors in the maintenance of immune tolerance in fetomaternal interface.

Keywords: T cell subsets; CD4⁺T cells; CD8⁺T cells; Treg; maternal-fetal immunity; pregnancy

OPEN ACCESS

*Correspondence:

Meirong Du, Laboratory for Reproductive Immunology, Hospital of Obstetrics and Gynecology, Fudan University Shanghai Medical College, Zhaozhou Rd.413, Shanghai, China, E-mail: mrdu@fudan.edu.cn

Received Date: 10 Jan 2018

Accepted Date: 07 Mar 2018

Published Date: 14 Mar 2018

Citation:

Lin Y, Zhang D, Du M. The Regulation and Function of T Lymphocyte in Fetomaternal Immunity Tolerance. *Ann Gynecol Obstetr Res.* 2018; 1(1): 1001.

Copyright © 2018 Du M. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

The crucial paradox about reproductive success is the coordinated interaction between paternally inherited antigens carried by the semi-allogeneic fetus and leukocytes infiltrating the maternal decidua [1-3]. Tremendous amounts of studies over the last two decades have revealed multiple mechanisms that enable the conceptus to avoid immunological destruction, including maternal T lymphocytes-mediated immune escape of fetal antigens from the mother immune system [1,4].

Decidual $\alpha\beta$ T cells, which are the most concerned study object, account for 10% of leukocytes in the first-trimester human decidua [1,2,5,6] and their proportion in decidual immunocyte rises along with the course of pregnancy [7,8]. The existence of multiple $\alpha\beta$ T cell subsets is endowed with diverse sets of functions. They orchestrate the physiological process of pregnancy through complicated interactions with extravillous trophoblast cells (EVTs), decidual stromal cells (DSCs) and other decidual immune cells (DICs), including nature killer cells (NK), macrophages, and dendritic cells (DC). The proportions and characteristics can be influenced by extracellular signal and pregnancy associated hormones [5,9-13].

In this review, we aim to generalize the current researches about the functions of decidual T cells and elucidate the interactive network among T cell subsets, DSC and trophoblasts regulated by immune-regulatory molecules and endocrine factors.

T Cells Subsets at the Maternal-fetal Interface

The proportion of CD3⁺TCR $\alpha\beta$ ⁺T cells which we concerned is about 10% in the first-trimester human decidua. 30-45% of these cells are CD4⁺T cells and 45-75% are CD8⁺T cells [1,2], while other T cells such as CD3⁺TCR $\gamma\delta$ ⁺T cells and CD4⁻CD8⁻TCR $\alpha\beta$ ⁺T cells are rare in decidua [14]. The subsets of effector T cells are Th1, Th2, Th17, regulatory T cells (Treg), and cytotoxic T lymphocytes

(CTLs), which are effector CD8⁺T cells. They are defined by distinctive transcription factors to maintain their differentiated state, as well as by the set of cytokines that mediate their effector functions[15]. Th1 cells comprise 5-30% of the first-trimester decidual CD4⁺T cells, whereas Th2 and Th17 cells comprise 5% and 2%, respectively analyzing by chemokine receptor expression pattern[16].

Th1 cells express the transcription factors T-bet and STAT4, and secrete interferon- γ (IFN- γ) as their signature cytokines. They also produce TNF- α to promote inflammation. Th1 cells express the chemokine receptors CXCR3 and CCR5. Th1 can eradicate the intracellular pathogens and virus-infected cells within peripheral tissues. Th1 are generally considered as major threats to fetal survival and participate in pregnancy pathologies. Whether augmented Th1-type immunity or suppressed Th1-type immunity at maternal-fetal interface can deteriorate the process of pregnancy[9].

Th2 express the transcription factors GATA3 and STAT6, secrete the cytokines IL-4, IL-5, IL-10 and IL-13, and preferentially express the chemokine receptor CCR4. The main function of Th2 in periphery is helping antibody isotype switching in allergic reactions and the prevention of helminths infection. In decidua, these cells provide an alternative, less potentially embryotoxic differentiation state for CD4⁺T cells in comparison to Th1 cells and have antagonism embryo cytotoxic effect with Th1[17], since data exist linking spontaneous abortion with increased decidual Th1 bias[9,18]. Skewing T cell toward a Th2 phenotype seems to be crucial in maternal immune adaption, yet underlying mechanisms remain a great extent obscure. Th2 cytokine profiles contribute to implantation of the embryo, development of the placenta, and survival of the fetus[19-21].

Th17 cells can express the transcription factors ROR γ t, STAT3 and IRF4, and secrete IL-17, IL-22. The predominant chemokine receptor of Th17 cells is CCR6. In periphery, Th17 can augment acute inflammatory responses, recruit neutrophils and mediate host immunity against extracellular bacteria and fungi. Th17 cells might play a role to induce protective immune response against extracellular microbes. While the overstimulation of Th17 may cause pregnant failure[22].

Tregs are defined by their expression of the transcription factor Foxp3, and are identified by the CD4⁺CD25^{hi} surface phenotype. 5% of the CD4⁺T cells in decidua are CD25^{bright}Foxp3⁺Tregs with immunosuppressive functions[5]. The cells express a wide variety of chemokine receptors, secrete immunosuppressive cytokines IL-10 and TGF- β . CD25⁺CD4⁺Treg cells can be generated in the thymus (tTreg, also called natural Treg or nTreg) or induced peripherally from naive CD4⁺T cells (pTreg, also referred to as iTreg)[15]. Treg cells play important roles in tumor immune escape. Accumulating evidences show the increase of these cells at the maternal-fetal interface during both human and mouse pregnancy [23].

Cytotoxic lymphocytes (CTLs) are present at the maternal/fetal interface in term gestations prelabor, where they express perforin and granzyme B [24]. They express the same profile of transcription factors (T-bet and STAT4) and cytokines (IFN- γ and TNF- α) as Th1 cells and express T-cell chemokine receptors (CXCR3 and CCR5).

The Regulation of Th1/Th2 Cytokines in Maternal-fetal Tolerance

It has long been established that a bias from the Th1 cytokine profile towards the Th2 profile, which called Th2 bias, contributes to

successful pregnancy maintenance. The predominant Th2 response is existed both in decidual microenvironment and the peripheral blood during early pregnancy [5]. The Th2 cytokine production and a Th1-to-Th2 shift at the maternal-fetal interface may be of greater significance than peripheral Th2 immunity. Th1-dominant immunity appears to endanger normal pregnancy. In contrast, Th2-dominant immunity offers important benefits, including protection of the developing embryo from immune rejection by the mother. The aberrant Th1:Th2 profile is associated with recurrent spontaneous abortion and preeclampsia [17,25]. Myeloid-derived suppressor cells (MDSCs) increase in peripheral blood of pregnant women, which are innate immune cells well studied in tumorigenesis, can mediate T cell suppression. Placenta derived MDSCs polarize CD4⁺T cells toward a Th2 differentiation to protect the pregnancy [26]. Various therapeutic strategies on promoting and maintaining Th2 predominant have been studied in order to avoid the early fetal loss [17].

Chemokines in regulation of Th2 bias

Chemokines can regulate the polarization of immune responses during pregnancy. Th2 chemokine, CCL17, is produced by trophoblasts, DSCs and endometrial gland cells, and regulates the infiltration of Th2 lymphocytes into the human decidua during early pregnancy [25].

The chemokine CCL2 secreted by DSCs or human recombinant CCL2 can enhance Th2 cytokines production (IL-4, IL-10) and GATA-3 transcription. Simultaneously, it inhibited the secretion of Th1 cytokines (TNF- α , IFN- γ) and decreased T-bet mRNA level. Furthermore, Th2 cytokines (IL-4,IL-10), rather than Th1 cytokines, was shown to increase CCL2 secretion of DSC [27]. DSCs secrete high levels of CCL2, and CCR2 is highly expressed in human DICs. The DSC-derived CCL2 interacts with CCR2 on DICs, leading to the production and secretion of Th2-type cytokines.

The CXCL12/CXCR4 axis is also involved in the maintenance of Th2 bias at the maternal/fetal interface[28]. CXCL12 can promote the production of Th2 cytokines while inhibiting Th1 cytokine production from DICs, which can be reversed by an anti-CXCR4 antibody. At the maternal-fetal interface, anti-CXCR4 antibody can upregulate Th1-type cytokines while downregulate Th2-type cytokines[6]. Dysregulation of this axis impairs the function of trophoblast cells and attenuate the cross-talk between trophoblasts and other decidual T cells [29,30]. Finally the disorder of Th1/Th2 balance contributes to miscarriage and fetal growth restriction, implying a critical role for this CXCL12/CXCR4 axis in the fetomaternal microenvironment [31,32].

Costimulatory molecules in regulation of Th2 bias

The expression of CD86 and CD28 in decidual tissues showed a significant positive correlation with the Th1 cytokine production (IL-2 and IFN- γ). While the expression of Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) on the decidual T cells showed a significant negative correlation with the Th1 cytokine production [10,33]. An increased expression of CD28 and CD86 was accompanied by a decreased expression of CTLA-4 on miscarriage compared with normal early pregnancy. The upregulation of CD86 on T cells might form an abnormal immune microenvironment, conducting to a shift to Th1 responses [34].

The Inducible T-Cell Co-Stimulator (ICOS) (expressed on placental T cells)/B7h (expressed in placental decidua) co-stimulatory pathway plays a critical role in maintaining the equilibrium at the

fetomaternal interface [10,35]. After crossing the female mice CBA/CaJ(CBA) and male C57BL/6(B6), pregnant females were injected with anti-mouse B7h mAb at 6.5, 8.5, 10.5, and 12.5 dpc. Locally in the placenta, levels of regulatory markers such as indoleamine 2,3-dioxygenase (IDO) and TGF- β 1 were reduced after anti-B7h monoclonal antibody treatment, whereas levels of effector cytokines (eg, IFN- γ) were significantly increased[35]. In addition, the programmed cell death 1(PD1)/Programmed cell death 1 ligand 1(PD-L1) and T-Cell Immunoglobulin Mucin Family Member 3 (Tim-3)/galectin-9 pathways involved in suppressing immune surveillance during tumorigenesis and progression, are also contributed to Th2-type responses at fetomaternal interface and maintain pregnancy by regulating CD4⁺ T cells function at the maternal-fetal interface [36-41].

Trophoblasts, DSCs, and DCs in regulation of Th2 bias

Trophoblasts, decidual and amnion member cells produce Th2-type cytokines, such as IL-4, IL-10 and IL-13. This local production of Th2 cytokines inhibits Th1 cell development and Th1 cytokine production, thereby protecting the fetus and preventing rejection[6,25,42]. Trophoblasts can also secrete various regulatory factors, including TGF- β , Placental Protein 14(PP14), Thrombospondin-1, galectin-1, inhibiting Th1 immunity and improving Th2 immunity. It indicates these cells are potential to be an important regulator on Th2 bias at the maternal/fetal interface[42]. It was reported that co-culture of trophoblasts and T cells results in an increase in the Th2 transcription factors GATA-3 and STAT-6, and a reduction in the Th1 transcription factor STAT-4 and subsequently decreased production of IFN- γ and TNF- α [6,17,42,43]. Thymic stromal lymphopoietins (TSLPs), a member of the IL-7 cytokine family, are mainly produced by thymic epithelial cells[44]. In thymus, TSLP-activated dendritic cells (TSLP-DCs) promote differentiation of CD4⁺FOXP3⁻ thymocytes into CD4⁺FOXP3⁺Tregs[45]. However, thymic function is inhibited by steroid hormones during pregnancy. Interestingly, a new research found human trophoblasts and decidual epithelial cells in materno-fetal interface of early placentas produce TSLP [43]. Human decidual DCs (dDCs) highly express the functional TSLP receptor complex. Furthermore, TSLP-activated dDCs prime decidual CD4⁺T cells for Th2 cell differentiation, favoring Th2 cell responses and maternal-fetal immunotolerance[43,46,47]. It was reported that decidual NKT cells may disrupt the local Th1/Th2 balance and result in abortion. NKT has the negative correlation with Th2 bias. Increased NKT cells in the decidua and peripheral blood can stimulate Th1 skew[48]. DSCs, the main constituent cells of decidua, are an endogenous source of IL-33. DSC-derived IL-33 can regulate cytokine production to Th2 bias response via its receptor ST2 expressed on dNKs and the NF- κ B pathway[49].

Pregnancy-related hormones in regulation of Th2 bias

Pregnancy-associated-hormones such as progesterone, oestradiol and human chorionic gonadotrophin (hCG) and thyroid hormones all promote Th2 bias[17,42,50]. Progesterone treatment can increase the production of Th2 type cytokine interleukin (IL)-4 and IL-5. Furthermore, progesterone was able to induce the production of the Th2 cytokines from established Th1 cell lineage. *In vitro*, progesterone was able to increase the mRNA expression and production of IL-4 in established Th1 clones[25,51]. It was reported that dydrogesterone (6-dehydro-9 β , 10 α -progesterone), the more potent and orally bioavailable progestogen, upregulates IL-4 and downregulates IFN- γ in PHA-stimulated PBMCs more significantly than progesterone *in*

vitro[52]. The study by He, et al. showed that estrogen, progesterone and hCG induce Th2 bias via upregulating the expression of CCL2/CCR2 [27,53].

Thyroid hormones can also be the crucial regulators during pregnancy, which dysfunction may lead to infertility and miscarriage[50,54,55]. Several studies show thyroid autoimmunity is associated with dominant Th1 immunity[56] and women with thyroid autoimmunity is associated with a threefold to fivefold increase in overall miscarriage rate[57-59].

The combined effect between these pregnancy-associated-hormones can reinforce the influence on pregnancy outcome. In normal gestation, increased estrogen and hCG upregulate thyroxine binding globulin (TBG), which in turn reduces circulating free T4 (FT4)[54]. Women with thyroid autoimmunity have higher abortion risk caused by hormonal changes during subsequent pregnancy. Several researches verified cross-reactivity between hCG, thyroid-stimulating hormone(TSH) and their corresponding receptors[50,60]. Anti-TSH receptor autoimmunity can attenuate the expression and function of hCG, which is another mechanism to explain the increased frequency of first-trimester miscarriage in women with thyroid autoimmunity[61].

The Regulation of Th17 Cells on Maternal-fetal Tolerance

Th17 cells play a central role in inflammation, autoimmunity and allergy. Accumulating evidence indicates that Th17 cells regulate pregnancy immunity [9,42]. Th17 cells and local inflammation can exist at the maternal-fetal interface during natural allogenic pregnancies [1,5,62,63]. Excess inflammatory responses and related cytokines induced by Th17 cell can result in recurrent pregnancy loss and pre-eclampsia[22,64-66], but mild inflammation can be effectively controlled through regulatory mechanisms to maintain successful pregnancy[67]. Thus, suppression of strong inflammatory responses is essential to ensure normal pregnancy[62,68]. Whether Th17 cells play a deleterious role in fetomaternal tolerance or augment the anti-infection immune responses to protect pregnancy still remains to be determined[35,67].

Co-stimulatory molecules and progesterone in regulation of Th17

PD1/PD-L1 is a negative co-stimulatory pathway demonstrated in many studies focused on tumor immunity. PD-1 is primarily expressed by lymphocytes. PD1/PD-L1 can induce an inhibitory signal to PD1⁺ T cells and drive them into rest state. In decidua, PD-L1 is constitutively expressed by DSCs and trophoblast. Some researches discover the PD1/PD-L1 pathway may be a critical mechanism for modulating Th17.

PD-L1 blockade can induce a shift towards higher frequency of Th17 cells, leading to a reduction in fetal survival and increase in the fetal resorption in a transgenic mouse model. However, neutralization of IL-17 can abrogate the anti PD-L1 effect on fetal survival rate[38,69]. ICOS-B7 signaling has been reported to play a crucial role in Th17 differentiation [70]. While some studies did not find any significant differences in decidual IL-17 production after B7 blockade [35]. Tim-3, a typical receptor of galectin-9(Gal-9), is reported to be extensively expressed by decidual NK cells, DSCs, and trophoblast cells. The expression of Tim-3 on lymphocytes can be upregulated by trophoblast cells and pregnancy associated

hormones[71-73]. Increasing evidence proves that the engagement of Tim-3/Gal-9 pathway leads to the death of Th17 cells and dampen the Th17 driven immune responses [39].

Progesterone has an inhibitory effect on suppressing the differentiation of naive cord blood T cells into inflammation-associated Th17 cells. It decreased STAT3 activation in response to IL-6, which is in line with the selective activity of progesterone in generation of Th17 cells [74].

Trophoblast, DSCs, and DICs in regulation of Th17

DSCs express CCR6, a chemokine receptor essential for Th17 cells migration, thereby recruiting peripheral Th17 cell into decidua[1,75]. The CCR2/CCL2 interaction also has an important role in migration of Th17 cells into maternal/fetal interface. Trophoblast cells, on the other hand, may downregulate the production of chemokines which are specific to Th17 migration. They can also suppress the expression of chemokine receptors on Th17 cells by producing regulatory molecules [42,67]. The cooperation between DSCs and trophoblasts help to sustain the homeostasis of Th17 cells in decidua.

Natural killer (NK) cells accumulate at the maternal-fetal interface in large numbers [2]. It was reported that Th17 cells can be inhibited by decidual NK cells via IFN- γ secreted by the decidual CD56brightCD27⁺NK subset in order to promote immune tolerance and successful pregnancy [62,64,76]. Treg cells can also regulate Th17 through cell-to-cell contact and immunosuppressive cytokines [65]. The imbalance of Th17/Treg may lead to implantation failure and other pregnancy disorders[22,66]. Treg can switch into a Th17-like phenotype when stimulated by allogeneic antigen-presenting cells as demonstrated in the follow[64].

The Regulation of Treg on Maternal-fetal Tolerance

Many studies have indicated that the abnormal pregnancy is associated with blunted maternal Treg expansion [5,23]. Recent data indicate that Treg cells specific to fetal antigens expand more than 100-fold during mouse pregnancy [23]. The systemic ablation of Tregs by targeting Foxp3⁺ cells leads to elevated rate of spontaneous fetal loss [23,77].

The role of Treg cells in fetomaternal tolerance was initially suggested by several lines of evidence. First, it was found that the replenishment of T cell-deficient female mice with Treg cell-depleted T cell populations before mating led to high levels of embryo resorption at mid-gestation when the females were mated to allogeneic males but not after mating with syngeneic males[12]. Second, it was found that the adoptive transfer of Treg cells attenuated the high rates of spontaneous fetal loss in pregnancy CBA/J females mated with DBA/2J males [78]. Furthermore, antigen-specific expansion of Tregs is observed in T cell receptor transgenic pregnant mice [10,12,79].

The regulation of Treg on Th1/Th2/Th17/CTL paradigm during pregnancy

Treg can hinder conceptus-specific T cells, including Th1, Th17, CTLs, to be activated during pregnancy via dominant immunosuppression[80]. Moreover, some studies suggest a direct interaction between Treg and DCs that renders the DCs into a tolerogenic phenotype that can in turn induce generation of Treg[81]. Treg cells strongly suppress the activation and proliferation of effector T cells. It was well understood that the mechanisms involved in the suppressive function of Treg cells were both cell-contact

dependent and cell-contact independent [82,83]. In the cell-contact dependent mechanism, Treg cells may kill responder T cells through several different ways including granzyme- and perforin-dependent mechanisms or by sending a negative signal to responder T cells. Activated Tregs may down-modulate the expression of CD80 and CD86 on APCs through the expression of IDO. The interaction of PD-1/PD-L1 in Treg cell also participates in mediating its immune suppression [12,38,83]. Recent studies have shown that Treg selectively up-regulate the immune regulatory molecule galectin-1. Galectin-1 can regulate T-cell activation, favoring the expansion of Treg[81,83,84]. In the cell-cell contact independent way, Treg can also mediate the immunosuppression by production of cytokines such as IL-10 and TGF- β [83].

The over-activation of Th1-type immunity can lead to pregnant failure. Treg cells play a part in this process to maintain a predominant Th2 environment [12]. Th17 cells might play a role in inducing protective immune response against extracellular microbes, conducting to successful pregnancy. However, excessive inflammation can cause embryo resorption. Treg cells might protect the embryo via extinguishing excessive inflammation in the uterus during pregnancy. In addition, there is a subtype of Th17/Treg intermediate cell, which express both RORC and Foxp3. The differentiation of both Th17 and Treg cells requires TGF- β . These two subsets can converse mutually under the help of IL-6 [5,9]. The imbalance of Th17/Treg ratio has been found in the cases of preeclampsia and spontaneous abortion [22,64,65].

Th1, Th2, Th17, and Treg cells can influence (enhance or suppress) the CD8⁺T cell response by secreting cytokines, such as IL-2 (Th1), IFN- γ (Th1), IL-4 (Th2), IL-17 (Th17), or IL-10 (Th2, Treg). Some Treg cell subsets can also provide cell-cell contact dependent inhibition of CD8⁺ T cell activation and proliferation[85]. The cross-talk among Th1 cells, Th2 cells, Th17 cells, CTLs and Treg cells is crucial for maintenance of a successful pregnancy and should be further explored to acquire a deeper understanding of fetomaternal tolerance.

Immune regulatory molecules in regulation of Treg during pregnancy

There is plenty of evidence that associates the early expansion of Treg pool with the exposure to seminal fluid[86-88]. Furthermore, seminal fluid contains potent immune suppressive molecules that contribute to Treg induction or conversion of conventional T cells into Treg, such as TGF- β and PGE-2-related prostaglandins in the plasma fraction. Co-culture of EVT with CD4⁺T cells can also increase the frequency of Foxp3⁺Treg cells [3]. Tryptophan catabolism and kynurenine production by IDO and T cell inhibition by PD-L1 pathway have both been implicated in Treg cell generation. The IDO-deficient females have shown reproductive defects when mated with IDO-deficient allogeneic males [89]. Some studies have been able to document the increased expression of PD-L1 may be important in regulating CD4⁺T cell conversion into CD4⁺CD25⁺Tregs in presence of anti-CD3 and TGF- β [10,12]. However, the inter-relationships between these pathways are quite complex. CTLA-4 is a potent negative regulator of T cells, and its increased expression could play an important role in maintaining tolerance in the fetus-specific T cells. The data from a pregnant murine model has shown the percentage of CD4⁺T cells that express CTLA-4 is increased. Furthermore, most of the CTLA-4⁺CD4⁺T cells are also Foxp3⁺, suggesting that the CTLA-4-expressing CD4⁺T cells consists of Tregs[10].

The Regulation of CTLs at the Fetomaternal Interface

CD8⁺T cells are key cell subtype which provides protective immunity against viral infections during pregnancy. They are also the most important cells that can directly bind and respond to paternal MHC molecules (HLA-C in human) expressed by fetal trophoblast cells [12]. Recent studies, from both murine and human, have demonstrated the presence of fetal-specific decidual CD8⁺T cells at fetal-maternal interface[79,85]. A majority of these CD8⁺T cells are highly differentiated effector memory T cells with various functions [24,85,90]. Conceptus-specific CD8⁺T cells are mostly deleted, as is typically seen with TCR-stimulated T cells lacking co-stimulation [12]. In contrast, some studies found the alloreactive CD8⁺T cell population increased as pregnancy progressed [85].

HLA-DR, a late activation marker, compared to CD25 and CD69. Previous studies detected a subset of regional activated decidual CD8⁺ T cells existed in the first trimester, cause a large proportion of CD8⁺ T cells expressed HLA-DR[91,92]. Some researchers consider the activated CD8⁺ T cells can help to maintain the normal pregnant progression. Cause the activated lymphocytes are capable of secreting cytokines to balance other lymphocyte subsets and decrease the cytotoxicity of CD8⁺ T cells to impair placental proliferation and trophoblast invasion[93]. However, Patients with spontaneous recurrent miscarriage showed increased HLA-DR expression but decreased CD25 on decidual CD8⁺ T cells. These phenomenon was also detected in the patient peripheral blood[94]. The up-regulation of HLA-DR indicated a over-activation of CD8⁺T cells, which may increase the specific cytotoxicity[95]. Some data also indicated these over-activation can induce lymphocyte anergy and deficiency to regulation the pregnant environment, contributing to the pathogenesis of abortion[96].

CD103⁺CD8⁺ T cells are tissue-resident memory T cells, which have been identified in various tissue. They can enhance immunity against infection[97-99]. While several researches indicate CD103⁺CD8⁺ T cells have immunoregulation functions and can suppress immune responses *in vitro*[100].

During pregnancy a significantly higher proportion of CD103⁺CD28⁺CD8⁺T cells are found in decidual tissue and maternal peripheral blood[101,102]. The phenotype and functions of such CD8⁺ subtype are similar to Foxp3⁺Treg cells, which called CD8⁺ regulatory T cells. These CD8⁺regulatory T cells are independent of classical MHC class I but are dependent upon a CEA subfamily member and can be activated by trophoblasts.They secrete IL10 and efficiently suppress Ab production in an Ag-nonspecific manner by cell contact,which are beneficial for normal gestation [102,103].

EVTs are the most important cells to direct CD8⁺T cell response in maternal-fetal interface. EVT's lack expression of HLA-A and HLA-B molecules, which are the main cause of CD8⁺T cell mediated transplant rejection [90]. EVT's and other cells at the fetal-maternal interface can express inhibitory molecules including HLA-G, IDO, B7-H3, Tim3 molecules, directly inhibit or reduce CTL mediated cytotoxicity [39,104-106]. Th1, Th2, Th17, and Treg cells can also regulate the CD8⁺T cell response by secreting cytokines, such as IL-2 (Th1), IFN- γ (Th1), IL-4 (Th2), IL-17 (Th17), or IL-10 (Th2, Treg). Tregs can inhibit CD8⁺T cell activation and proliferation in decidua through cell-to-cell contact[85]. The presence of anti-inflammatory APCs in decidua, such as decidual macrophages (dMs):CD11c⁺ and

CD11c^{low}, may activate CD8⁺T cells to become immune regulatory cells[107]. At the post-transcriptional level, microRNAs, which have recently been shown to control effector memory T cell differentiation, can decrease the perforin and granzyme B proteins secreted by decidual CD8⁺ effector and effector memory cells[108].

Conclusions

The juxtaposition of the placenta and decidua creates the feto-maternal interface, where placental trophoblasts and uterine lymphocytes come into contact with each other. Decidual T cells, an important lymphocyte subset, should be well orchestrated to create a robust micro-environment which is beneficial for fetal survival. The coordination and suppression among these T cells and their interaction with DSCs, EVT's, and DICs form a complex regulatory network affected by immunoregulatory molecules and endocrine hormone. The regulatory network maintains homeostasis between the maternal immune system and the fetus. A deeper exploration about the network can help to acquire a better understanding of immune mechanisms on maternal-fetal tolerance and potential therapeutic prospect on pregnancy complications.

References

1. Nancy P, Erlebacher A. T cell behavior at the maternal-fetal interface. *Int J Dev Biol.* 2014;58(2-4):189-98.
2. Erlebacher A. Immunology of the Maternal-Fetal Interface. *Annu Rev Immunol.* 2013;31:387-411.
3. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. *Nat Immunol.* 2015;16(4):328-34.
4. Piccinini MP. T cell tolerance towards the fetal allograft. *J Reprod Immunol.* 2010;85(1):71-5.
5. Mjösberg J, Berg G, Jenmalm MC, Ernerudh J. FOXP3⁺ regulatory T cells and T helper 1, T helper 2, and T helper 17 cells in human early pregnancy decidua. *Biol Reprod.* 2010;82(4):698-705.
6. Piao HL, Tao Y, Zhu R, Wang SC, Tang CL, Fu Q, et al. The CXCL12/CXCR4 axis is involved in the maintenance of Th2 bias at the maternal/fetal interface in early human pregnancy. *Cell Mol Immunol.* 2012;9(5):423-30.
7. Kwan M, Hazan A, Zhang J, Jones RL, Harris LK, Whittle W, et al. Dynamic changes in maternal decidual leukocyte populations from first to second trimester gestation. *Placenta.* 2014;35(12):1027-34.
8. Wilczyński JR, Tchorzewski H, Banasik M, Glowacka E, Wiecek A, Lewkowicz P, et al. Lymphocyte subset distribution and cytokine secretion in third trimester decidua in normal pregnancy and preeclampsia. *Eur J ObstetGynecolReprod Biol.* 2003;109(1):8-15.
9. Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol.* 2010;63(6):601-10.
10. Perchellet AL, Jasti S, Petroff MG. Maternal CD4⁺ and CD8⁺ T Cell Tolerance Towards a Fetal Minor Histocompatibility Antigen in T Cell Receptor Transgenic Mice. *Biol Reprod.* 2013;89(4):102.
11. Schminkey DL, Groer M. Imitating a stress response: A new hypothesis about the innate immune system's role in pregnancy. *Med Hypotheses.* 2014;82(6):721-9.
12. Erlebacher A. Mechanisms of T cell tolerance towards the allogeneic fetus. *Nat Rev Immunol.* 2013;13(1):23-33.
13. Fu B, Tian Z, Wei H. Subsets of human natural killer cells and their regulatory effects. *Immunology.* 2014;141(4):483-9.
14. Tilburgs T, Claas FH, Scherjon SA. Elsevier Trophoblast Research Award Lecture: Unique properties of decidual T cells and their role in immune

- regulation during human pregnancy. *Placenta*. 2010;31 Suppl:S82-6.
15. Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. *Nat Med*. 2013;19(5):548-56.
 16. Mjösberg J, Berg G, Jenmalm MC, Ernerudh J. FOXP3⁺ regulatory T cells and T helper 1, T helper 2, and T helper 17 cells in human early pregnancy decidua. *BiolReprod*. 2010;82(4):698-705.
 17. Sykes L, MacIntyre DA, Yap XJ, Teoh TG, Bennett PR. The Th1:Th2 Dichotomy of Pregnancy and Preterm Labour. *MediatInflamm*. 2012;1-12.
 18. Piccinni MP, Beloni L, Livi C, Maggi E, Scarselli G, Romagnani S. Defective production of both leukemia inhibitory factor and type 2 T-helper cytokines by decidual T cells in unexplained recurrent abortions. *Nat Med*. 1998;4(9):1020-4.
 19. Dealtry GB, O'Farrell MK, Fernandez N. The Th2 cytokine environment of the placenta. *Int Arch Allergy Immunol*. 2000;123(2):107-19.
 20. Schutt C. [Maternal anti-paternal reactivity--depends on etiology]. *ZentralblGynakol*. 1999;121(4):202-5.
 21. Lin H, Mosmann TR, Guilbert L, Tuntipopipat S, Wegmann TG. Synthesis of T helper 2-type cytokines at the maternal-fetal interface. *J Immunol*. 1993;151(9):4562-73.
 22. Lee SK, Kim JY, Lee M, Gilman-Sachs A, Kwak-Kim J. Th17 and regulatory T cells in women with recurrent pregnancy loss. *Am J ReprodImmunol*. 2012;67(4):311-8.
 23. Rowe JH, Ertelt JM, Xin L, Way SS. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. *Nature*. 2012;490(7418):102-6.
 24. Tilburgs T, Schonkeren D, Eikmans M, Nagtzaam NM, Datema G, Swings GM, et al. Human Decidual Tissue Contains Differentiated CD8⁽⁺⁾ Effector-Memory T Cells with Unique Properties. *J Immunol*. 2010;185(7):4470-7.
 25. McFadden JP, Thyssen JP, Basketter DA, Puangpet P, Kimber I. T helper cell 2 immune skewing in pregnancy/early life: chemical exposure and the development of atopic disease and allergy. *Br J Dermatol*. 2015;172(3):584-91.
 26. Kostlin N, Hofstadter K, Ostermeier AL, Spring B, Leiber A, Haen S, et al. Granulocytic Myeloid-Derived Suppressor Cells Accumulate in Human Placenta and Polarize toward a Th2 Phenotype. *J Immunol*. 2016;196(3):1132-45.
 27. He Y, He X, Guo P, Du M, Shao J, Li M, et al. The decidual stromal cells-secreted CCL2 induces and maintains decidual leukocytes into Th2 bias in human early pregnancy. *ClinImmunol*. 2012;145(2):161-73.
 28. Piao HL, Wang SC, Tao Y, Fu Q, Du MR, Li DJ. CXCL12/CXCR4 signal involved in the regulation of trophoblasts on peripheral NK cells leading to Th2 bias at the maternal-fetal interface. *Eur Rev Med Pharmacol Sci*. 2015;19(12):2153-61.
 29. Quinn KE, Reynolds LP, Grazul-Bilska AT, Borowicz PP, Ashley RL. Placental development during early pregnancy: Effects of embryo origin on expression of chemokine ligand twelve (CXCL12). *Placenta*. 2016;43:77-80.
 30. Wang L, Li X, Zhao Y, Fang C, Lian Y, Gou W, et al. Insights into the mechanism of CXCL12-mediated signaling in trophoblast functions and placental angiogenesis. *ActaBiochimBiophys Sin (Shanghai)*. 2015;47(9):663-72.
 31. Lu J, Zhou WH, Ren L, Zhang YZ. CXCR4, CXCR7, and CXCL12 are associated with trophoblastic cells apoptosis and linked to pathophysiology of severe preeclampsia. *ExpMolPathol*. 2016;100(1):184-91.
 32. Zhang Y, Wang J, Gu Y, Li Y. [Relationship between the expression of chemokines and their receptors in the maternal-fetal interface and pathogenesis of unexplained recurrent spontaneous abortion]. *Zhonghua Fu Chan KeZaZhi*. 2015;50(8):608-13.
 33. Jin LP, Fan DX, Li DJ. Regulation of costimulatory signal in maternal-fetal immune tolerance. *Am J ReprodImmunol*. 2011;66(2):76-83.
 34. Jin LP, Fan DX, Zhang T, Guo PF, Li DJ. The costimulatory signal upregulation is associated with Th1 bias at the maternal-fetal interface in human miscarriage. *Am J ReprodImmunol*. 2011;66(4):270-8.
 35. Riella LV, Dada S, Chabtini L, Smith B, Huang L, Dakle P, et al. B7h (ICOS-L) Maintains Tolerance at the Fetomaternal Interface. *Am J Pathol*. 2013;182(6):2204-13.
 36. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann N Y Acad Sci*. 2011;1221:80-7.
 37. Sayama S, Nagamatsu T, Schust DJ, Itaoka N, Ichikawa M, Kawana K, et al. Human decidual macrophages suppress IFN- γ production by T cells through costimulatory B7-H1:PD-1 signaling in early pregnancy. *J ReprodImmunol*. 2013;100(2):109-17.
 38. Zhang YH, Tian M, Tang MX, Liu ZZ, Liao AH. Recent Insight into the Role of the PD-1/PD-L1 Pathway in Feto-Maternal Tolerance and Pregnancy. *Am J ReprodImmunol*. 2015;74(3):201-8.
 39. Meggyes M, Lajko A, Palkovics T, Totsimon A, Illes Z, Szereday L, et al. Feto-maternal immune regulation by TIM-3/galectin-9 pathway and PD-1 molecule in mice at day 14.5 of pregnancy. *Placenta*. 2015;36(10):1153-60.
 40. Shepard MT, Bonney EA. PD-1 regulates T cell proliferation in a tissue and subset-specific manner during normal mouse pregnancy. *Immunol Invest*. 2013;42(5):385-408.
 41. Moritoki M, Kadowaki T, Niki T, Nakano D, Soma G, Mori H, et al. Galectin-9 ameliorates clinical severity of MRL/lpr lupus-prone mice by inducing plasma cell apoptosis independently of Tim-3. *Plos One*. 2013;8(4):e60807.
 42. Liu F, Guo J, Tian T, Wang H, Dong F, Huang H, et al. Placental trophoblasts shifted Th1/Th2 balance toward Th2 and inhibited Th17 immunity at fetomaternal interface. *APMIS*. 2011;119(9):597-604.
 43. Guo PF, Du MR, Wu HX, Lin Y, Jin LP, Li DJ. Thymic stromal lymphopoietin from trophoblasts induces dendritic cell-mediated regulatory TH2 bias in the decidua during early gestation in humans. *Blood*. 2010;116(12):2061-9.
 44. Watanabe N, Wang YH, Lee HK, Ito T, Wang YH, Cao W, et al. Hassall's corpuscles instruct dendritic cells to induce CD4⁺CD25⁺ regulatory T cells in human thymus. *Nature*. 2005;436(7054):1181-5.
 45. Hanabuchi S, Ito T, Park WR, Watanabe N, Shaw JL, Roman E, et al. Thymic stromal lymphopoietin-activated plasmacytoid dendritic cells induce the generation of FOXP3⁺ regulatory T cells in human thymus. *J Immunol*. 2010;184(6):2999-3007.
 46. Rochman I, Watanabe N, Arima K, Liu YJ, Leonard WJ. Cutting edge: direct action of thymic stromal lymphopoietin on activated human CD4⁺ T cells. *J Immunol*. 2007;178(11):6720-4.
 47. Du MR, Guo PF, Piao HL, Wang SC, Sun C, Jin LP, et al. Embryonic Trophoblasts Induce Decidual Regulatory T Cell Differentiation and Maternal-Fetal Tolerance through Thymic Stromal Lymphopoietin Instructing Dendritic Cells. *J Immunol*. 2014;192(4):1502-11.
 48. Yuan J, Li J, Huang S, Sun X. Characterization of the subsets of human NKT-like cells and the expression of Th1/Th2 cytokines in patients with unexplained recurrent spontaneous abortion. *J ReprodImmunol*. 2015;110:81-8.
 49. Hu W, Huang L, Li M, Jin L, Li D, Zhu X. Decidual stromal cell-derived IL-33 contributes to Th2 bias and inhibits decidual NK cell cytotoxicity through NF- κ B signaling in human early pregnancy. *J ReprodImmunol*. 2015;109:52-65.

50. Toulis KA, Goulis DG, Venetis CA, Kolibianakis EM, Tarlatzis BC, Papadimas I. Thyroid autoimmunity and miscarriages: The corpus luteum hypothesis. *Med Hypotheses*. 2009;73(6):1060-2.
51. Raghupathy R, Al ME, Makhseed M, Al-Azemi M, Azizieh F. Redirection of cytokine production by lymphocytes from women with pre-term delivery by dydrogesterone. *Am J Reprod Immunol*. 2007;58(1):31-8.
52. He YY, Du MR, Guo PF, He XJ, Zhou WH, Zhu XY, et al. Regulation of C-C motif chemokine ligand 2 and its receptor in human decidual stromal cells by pregnancy-associated hormones in early gestation. *Hum Reprod*. 2007;22(10):2733-42.
53. Kim NY, Cho HJ, Kim HY, Yang KM, Ahn HK, Thornton S, et al. Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. *Am J Reprod Immunol*. 2011;65(1):78-87.
54. Mintzioti G, Anagnostis P, Toulis KA, Goulis DG. Thyroid diseases and female reproduction. *Minerva Med*. 2012;103(1):47-62.
55. Lichiardopol C, Mota M. The thyroid and autoimmunity. *Rom J Intern Med*. 2009;47(3):207-15.
56. Bellver J, Soares SR, Alvarez C, Munoz E, Ramirez A, Rubio C, et al. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. *Hum Reprod*. 2008;23(2):278-84.
57. Poppe K, Glinoe D, Tournaye H, Devroey P, van Steirteghem A, Kaufman L, et al. Assisted reproduction and thyroid autoimmunity: an unfortunate combination? *J Clin Endocrinol Metab*. 2003;88(9):4149-52.
58. Negro R, Formoso G, Coppola L, Presicce G, Mangieri T, Pezzarossa A, et al. Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: the role of autoimmunity and thyroid function. *J Endocrinol Invest*. 2007;30(1):3-8.
59. Bansal AS, Bora SA, Saso S, Smith JR, Johnson MR, Thum MY. Mechanism of human chorionic gonadotrophin-mediated immunomodulation in pregnancy. *Expert Rev Clin Immunol*. 2012;8(8):747-53.
60. Walkington L, Webster J, Hancock BW, Everard J, Coleman RE. Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. *Br J Cancer*. 2011;104(11):1665-9.
61. Fu B, Li X, Sun R, Tong X, Ling B, Tian Z, et al. Natural killer cells promote immune tolerance by regulating inflammatory TH17 cells at the human maternal-fetal interface. *Proceedings of the National Academy of Sciences* 2013;110(3):E231-40.
62. Vargas-Rojas MI, Solleiro-Villavicencio H, Soto-Vega E. Th1, Th2, Th17 and Treg levels in umbilical cord blood in preeclampsia. *J Matern Fetal Neonatal Med*. 2016;29:1-4.
63. Fu B, Tian Z, Wei H. TH17 cells in human recurrent pregnancy loss and pre-eclampsia. *Cell Mol Immunol*. 2014;11(6):564-70.
64. Saifi B, Rezaee SA, Tajik N, Ahmadpour ME, Ashrafi M, Vakili R, et al. Th17 cells and related cytokines in unexplained recurrent spontaneous miscarriage at the implantation window. *Reprod Biomed Online*. 2014;29(4):481-9.
65. Liu YS, Wu L, Tong XH, Wu LM, He GP, Zhou GX, et al. Study on the relationship between Th17 cells and unexplained recurrent spontaneous abortion. *Am J Reprod Immunol*. 2011;65(5):503-11.
66. Wu HX, Jin LP, Xu B, Liang SS, Li DJ. Decidual stromal cells recruit Th17 cells into decidua to promote proliferation and invasion of human trophoblast cells by secreting IL-17. *Cell Mol Immunol*. 2014;11(3):253-62.
67. Karimi K, Arck PC. Natural Killer cells: keepers of pregnancy in the turnstile of the environment. *Brain Behav Immun*. 2010;24(3):339-47.
68. D'Addio F, Riella LV, Mfarrej BG, Chabtni L, Adams LT, Yeung M, et al. The Link between the PDL1 Costimulatory Pathway and Th17 in Fetomaternal Tolerance. *J Immunol*. 2011;187(9):4530-41.
69. Paulos CM, Carpenito C, Plesa G, Suhoski MM, Varela-Rohena A, Golovina TN, et al. The inducible costimulator (ICOS) is critical for the development of human T(H)17 cells. *Sci Transl Med*. 2010;2(55):55ra78.
70. Li YH, Zhou WH, Tao Y, Wang SC, Jiang YL, Zhang D, et al. The Galectin-9/Tim-3 pathway is involved in the regulation of NK cell function at the maternal-fetal interface in early pregnancy. *Cell Mol Immunol*. 2016;13(1):73-81.
71. Wang SC, Li YH, Piao HL, Hong XW, Zhang D, Xu YY, et al. PD-1 and Tim-3 pathways are associated with regulatory CD8⁺ T-cell function in decidua and maintenance of normal pregnancy. *Cell Death Dis*. 2015;6:e1738.
72. Wang S, Zhu X, Xu Y, Zhang D, Li Y, Tao Y, et al. Programmed cell death-1 (PD-1) and T-cell immunoglobulin mucin-3 (Tim-3) regulate CD4⁺T cells to induce Type 2 helper T cell (Th2) bias at the maternal-fetal interface. *Hum Reprod*. 2016;31(4):700-11.
73. Lee JH, Ulrich B, Cho J, Park J, Kim CH. Progesterone Promotes Differentiation of Human Cord Blood Fetal T Cells into T Regulatory Cells but Suppresses Their Differentiation into Th17 Cells. *J Immunol*. 2011;187(4):1778-87.
74. Yu Q, Lou XM, He Y. Preferential recruitment of Th17 cells to cervical cancer via CCR6-CCL20 pathway. *PLoS One*. 2015;10(3):e0120855.
75. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol*. 2009;27:485-517.
76. Shima T, Sasaki Y, Itoh M, Nakashima A, Ishii N, Sugamura K, et al. Regulatory T cells are necessary for implantation and maintenance of early pregnancy but not late pregnancy in allogeneic mice. *J Reprod Immunol*. 2010;85(2):121-9.
77. Yin Y, Han X, Shi Q, Zhao Y, He Y. Adoptive transfer of CD4⁺CD25⁺ regulatory T cells for prevention and treatment of spontaneous abortion. *Eur J Obstet Gynecol Reprod Biol*. 2012;161(2):177-81.
78. Moldenhauer LM, Hayball JD, Robertson SA. Utilising T cell receptor transgenic mice to define mechanisms of maternal T cell tolerance in pregnancy. *J Reprod Immunol*. 2010;87(1-2):1-13.
79. Piccinni M, Lombardelli L, Logiodice F, Kullo O, Romagnani S, Le Bouteiller P. T helper cell mediated-tolerance towards fetal allograft in successful pregnancy. *Clin Mol Allergy*. 2015;13(1):9.
80. Than NG, Romero R, Kim CJ, McGowen MR, Papp Z, Wildman DE. Galectins: guardians of eutherian pregnancy at the maternal-fetal interface. *Trends Endocrinol Metab*. 2012;23(1):23-31.
81. La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: Regulatory T cells control maternal immune tolerance toward the fetus. *Immunol Lett*. 2014;162(1):41-8.
82. Leber A, Teles A, Zenclussen AC. Regulatory T Cells and Their Role in Pregnancy. *Am J Reprod Immunol*. 2010;63(6):445-59.
83. Blidner AG, Rabinovich GA. 'Sweetening' pregnancy: galectins at the fetomaternal interface. *Am J Reprod Immunol*. 2013;69(4):369-82.
84. Lissauer D, Piper K, Goodyear O, Kilby MD, Moss PA. Fetal-specific CD8⁺ cytotoxic T cell responses develop during normal human pregnancy and exhibit broad functional capacity. *J Immunol*. 2012;189(2):1072-80.
85. Robertson SA, Sharkey DJ. Seminal fluid and fertility in women. *Fertil Steril*. 2016;106(3):511-9.
86. Schjenken JE, Robertson SA. Seminal Fluid Signalling in the Female Reproductive Tract: Implications for Reproductive Success and Offspring Health. *Adv Exp Med Biol*. 2015;868:127-58.
87. Schumacher A, Zenclussen AC. The Paternal Contribution to Fetal Tolerance. *Adv Exp Med Biol*. 2015;868:211-25.

88. Huang L, Baban B, Johnson BR, Mellor AL. Dendritic cells, indoleamine 2,3 dioxigenase and acquired immune privilege. *Int Rev Immunol*. 2010;29(2):133-55.
89. Tilburgs T, Strominger JL. CD8⁺ Effector T Cells at the Fetal-Maternal Interface, Balancing Fetal Tolerance and Antiviral Immunity. *Am J Reprod Immunol*. 2013;69(4):395-407.
90. Ho HN, Chao KH, Chen CK, Yang YS, Huang SC. Activation status of T and NK cells in the endometrium throughout menstrual cycle and normal and abnormal early pregnancy. *Hum Immunol*. 1996;49(2):130-6.
91. Saito S, Nishikawa K, Morii T, Narita N, Enomoto M, Ichijo M. Expression of activation antigens CD69, HLA-DR, interleukin-2 receptor-alpha (IL-2R alpha) and IL-2R beta on T cells of human decidua at an early stage of pregnancy. *Immunology*. 1992;75(4):710-2.
92. Chao KH, Wu MY, Chen CD, Yang JH, Yang YS, Ho HN. The expression of killer cell inhibitory receptors on natural killer cells and activation status of CD4⁺ and CD8⁺ T cells in the decidua of normal and abnormal early pregnancies. *Hum Immunol*. 1999;60(9):791-7.
93. Carbone J, Gallego A, Lanio N, Chean C, Navarro J, Sarmiento E. Peripheral blood CD8⁺DR⁺ T-cell count: a potential new immunologic marker of unexplained recurrent abortion. *FertilSteril*. 2010;94(1):360-1.
94. Kuon RJ, Schaumann J, Goeggl T, Strowitzki T, Sadeghi M, Opelz G, et al. Patients with idiopathic recurrent miscarriage show higher levels of DR⁺ activated T-cells that are less responsive to mitogens. *J Reprod Immunol*. 2015;112:82-7.
95. Sindram-Trujillo A, Scherjon S, Kanhai H, Roelen D, Claas F. Increased T-cell activation in decidua parietalis compared to decidua basalis in uncomplicated human term pregnancy. *Am J Reprod Immunol*. 2003;49(5):261-8.
96. Pauls K, Schon M, Kubitzka RC, Homey B, Wiesenborn A, Lehmann P, et al. Role of integrin alphaE(CD103)beta7 for tissue-specific epidermal localization of CD8⁺ T lymphocytes. *J Invest Dermatol*. 2001;117(3):569-75.
97. Schenkel JM, Fraser KA, Vezys V, Masopust D. Sensing and alarm function of resident memory CD8⁺ T cells. *Nat Immunol*. 2013;14(5):509-13.
98. Gebhardt T, Wakim LM, Eidsmo L, Reading PC, Heath WR, Carbone FR. Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus. *Nat Immunol*. 2009;10(5):524-30.
99. Allez M, Brimnes J, Dotan I, Mayer L. Expansion of CD8⁺ T cells with regulatory function after interaction with intestinal epithelial cells. *Gastroenterology*. 2002;123(5):1516-26.
100. Tilburgs T, Roelen DL, van der Mast BJ, van Schip JJ, Kleijburg C, de Groot-Swings GM, et al. Differential distribution of CD4(+)CD25(bright) and CD8(+)CD28(-) T-cells in decidua and maternal blood during human pregnancy. *Placenta*. 2006;27Suppl A:S47-53.
101. Shao L, Jacobs AR, Johnson VV, Mayer L. Activation of CD8⁺ regulatory T cells by human placental trophoblasts. *J Immunol*. 2005;174(12):7539-47.
102. Tilburgs T, Scherjon SA, Roelen DL, Claas FH. Decidual CD8⁺CD28⁻ T cells express CD103 but not perforin. *Hum Immunol*. 2009;70(2):96-100.
103. Amodio G, Sales de Albuquerque R, Gregori S. New insights into HLA-G mediated tolerance. *Tissue Antigens*. 2014;84(3):255-63.
104. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol*. 2004;4(10):762-74.
105. Petroff MG, Kharatyan E, Torry DS, Holets L. The immunomodulatory proteins B7-DC, B7-H2, and B7-H3 are differentially expressed across gestation in the human placenta. *Am J Pathol*. 2005;167(2):465-73.
106. Houser BL, Tilburgs T, Hill J, Nicotra ML, Strominger JL. Two unique human decidual macrophage populations. *J Immunol*. 2011;186(4):2633-42.
107. Wu T, Wieland A, Araki K, Davis CW, Ye L, Hale JS, et al. Temporal expression of microRNA cluster miR-17-92 regulates effector and memory CD8⁺ T-cell differentiation. *Proc Natl Acad Sci U S A*. 2012;109(25):9965-70.