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The Regulation and Function of T Lymphocyte in Fetomaternal Immunity Tolerance

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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

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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].

DecidualαβT 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 decidualimmunocyte rises along with the course of pregnancy[7,8]. The existence of multiple αβT cell subsets is endowed with diverse sets of functions. They orchestrate the physiological process of pregnancy through complicated interactions with extravilloustrophoblast 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 RORγt, 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 $CD4^+CD25hi$ surface phenotype. 5% of the $CD4^+$T cells in decidua are $CD25brightFoxp3^+$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. Simutaneously, 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, conducing 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-β1 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 DICs in regulation of Th2 bias

Trophoblasts, decidual and amnia 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. Futhermore, 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 regulates cytokine production to Th2 bias response via its receptor ST2 expressed on dNKs and the NF-κB 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 Thl clones[25,51]. It was reported that dydrogesterone (6-dehydro-9β, 10α-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 theses pregnancy-associated-hormones can reinforce the influence on pregnancy outcome. In normal gestation, increased estrogen and hCGupregulatethyroxine 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 existed 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

hormomes[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, conducing 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 EVTs 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 propotion 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 HLR-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 similiar 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 benificial for normal gestation [102,103].

EVTs are the most important cells to direct CD8⁺T cell response in maternal-fetal interface. EVTs lack expression of HLA-A and HLA-B molecules, which are the main cause of CD8⁺T cell mediated transplant rejection [90]. EVTs 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):CD11chi and CD11clow, 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, EVTs, 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.

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