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REVIEW

Beyond Immune Balance: The Pivotal Role of Decidual Regulatory T Cells in Unexplained Recurrent Spontaneous Abortion

Qing-Hui Li[1,2], Qiu-Yan Zhao[1], Wei-Jing Yang[1], Ai-Fang Jiang[2], Chun-E Ren[2], Yu-Han Meng[2]

[1]School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, 261021, People's Republic of China; [2]Center of Reproductive Medicine, Affiliated Hospital of Shandong Second Medical University, Weifang, Shandong, 261000, People's Republic of China

Correspondence: Yu-Han Meng, Center of Reproductive Medicine, Affiliated Hospital of Shandong Second Medical University, No. 2428.Yuhe Road, Kuiwen District, Weifang, Shandong, 261031, People's Republic of China, Tel/Fax +86 536-3081389, Email yhmeng6@163.com

Abstract: Recurrent spontaneous abortion (RSA) is defined as two or more consecutive pregnancy failures, which brings tremendous stress to women of childbearing age and seriously affects family well-being. However, the reason in about 50% of cases remains unknown and is defined as unexplained recurrent spontaneous abortion (URSA). The immunological perspective in URSA has attracted widespread attention in recent years. The embryo is regarded as a semi-allogeneic graft to the mother. A successful pregnancy requires transition to an immune environment conducive to embryo survival at the maternal–fetal interface. As an important member of regulatory immunity, regulatory T (Treg) cells play a key role in regulating immune tolerance at the maternal–fetal interface. This review will focus on the phenotypic plasticity and lineage stability of Treg cells to illustrate its relationship with URSA.

Keywords: immune homeostasis, Treg cells, phenotype, maternal–fetal tolerance

Introduction

Immune self-stabilization is one of the three functions of human immune system.[1] Regulatory T (Treg) cells are named for their powerful function in regulating the immune system and improving immunological self-tolerance, which plays an important role in immune homeostasis.[2,3] Treg cells have been confirmed to be related to various immunological diseases such as rheumatoid arthritis (RA), type 1 diabetes, allergy and graft-versus-host disease (GVHD).[4–7] In recent years, substantial evidence has shown that Treg cells play a major role in fetal-maternal tolerance.[8–10] Treg cells not only suppress inflammation but also prevent the adverse effects of anti-fetal alloantigen, facilitating essential vascular adaptations crucial for placental morphogenesis at the maternal–fetal interface.[11–14] In the first trimester of human pregnancy, T cells comprise 10% to 20% of decidual immune cells,[15] of which Treg cells account for 10–30% of the $CD4^+$ T cells.[16,17] Phenotypic plasticity is an important characteristic of Treg cells, and lineage stability of Treg cells is crucial for their function. Since the 1970s, scholars have made efforts to characterize Treg cells by reliable molecular markers.[18] In the mid-1990s, Sakaguchi et al discovered that Treg cells constitutively and highly expressed CD25.[19] In 2003, transcription factor Fork head box P3 (FoxP3) was found specifically expressed in $CD25^+CD4^+$ natural Treg cells in rodents and human,[20–22] which is a key determinant of their suppressive function. Subsequently, in order to better elucidate its function and heterogeneity, more and more markers have been found to characterize its phenotype, such as Helios, neuropilin-1 (Nrp-1), inducible co-stimulator (ICOS), programmed cell death protein 1 (PD-1), ITIM domain protein (TIGIT) and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), etc.[23–27] However, phenotypic plasticity and lineage stability of Treg cells is still a controversial topic.

Recurrent spontaneous abortion (RSA) is defined as two or more consecutive pregnancy failures according to the guidelines of the American Society of Reproductive Medicine.[28] A lot of evidence indicates that RSA is related to genetic defects, immune disorders, abnormal genital structure, specific and nonspecific inflammation, endocrine disorders and other factors.[29–32] The etiology of RSA is complex, and more than 50% of patients are unknown.[33] As the number of

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miscarriages increases, the likelihood of URSA women experiencing early miscarriage, premature birth, placenta previa and other related complications also increase when they become pregnant again.[34,35] This can be serious adverse effects on women with URSA. In recent years, the immunological perspective in recurrent miscarriage (RM) has attracted widespread attention. Successful pregnancy requires the attachment of the embryo to the endometrium, decidualization of the endometrium, and the differentiation of blastocysts into trophoblasts to invade the decidua.[10,36] Abundant immune cells reside in the decidua in close contact with paternally derived alloantigens and fetal tissues. They participate in the establishing, sustaining and terminating pregnancy extensively.[10] As a member of regulatory immunity, the significance of Treg cells during the implantation and maintenance of the healthy pregnancy is evident. However, the role of Treg cells in URSA is still a topic worthy of further study. This review delves into the phenotypic plasticity and lineage stability of Treg cells and elucidates the relationship between Treg cell functions and URSA, aiming to present novel insights for immunological approaches to treating URSA.

Classification of Treg Cells

According to differentiation, Treg cells can be categorized into two groups: natural Treg (nTreg) cells and induced Treg (iTreg) cells. During thymus development, immature T lymphocytes produce nTreg cells, identified by the presence of $CD4^+CD25^+Foxp3^+$ T cells. Conversely, mature $CD4^+CD25^-$ T cells can convert into iTreg cells under stimulation of peripheral antigen or induction of immunosuppressive factors. iTreg cells can be divided into Type 1 regulatory T (Tr1) and Th3 subsets. Tr1 Treg cells mainly produce interleukin (IL)-10, while Th3 cells primarily secrete transforming growth factor beta (TGF-β).[4,37]

In recent years, scholars have recommended that Treg cells can be classified into two categories according to their origins. The aforementioned nTreg cells may be termed thymus-derived Treg (tTreg) cells, originating from the thymus with a T-cell receptor (TCR) featuring relatively high self-affinity.[38] Periphery-derived Treg (pTreg) cells develop from $CD4^+$ effector cells under TCR signal transduction or other factors (such as TGF-β, IL-2),[39] which mainly exist in peripheral barrier tissues and play an important role in controlling local inflammation.[40]

According to the function and location, Treg cells can also be divided into central Treg (cTreg) cells and effector Treg (eTreg) cells.[41] cTreg cells, expressing CC-chemokine receptor (CCR) 7 and L-Selectin (CD62L) at high levels, are mainly located in peripheral lymphoid tissue.[42] eTreg cells are mainly found in non-lymphoid tissues and can be identified by the presence of surface markers like ICOS or CD44.[43] They exhibit a remarkable ability to adapt and specialize to specific tissue environments.[44,45]

Immunosuppressive Mechanism of Treg Cells

The immunosuppressive effect of Treg cells is primarily accomplished through the interaction of their inhibitory surface molecules with other immune cells. TIGIT presented on Treg cells interacts with CD155 on dendritic cells (DCs) to suppress the activation of effector T cells (Teffs), Th1, and Th17, which is achieved by IL-10 augmentation and IL-12 reduction.[46–49] Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) on Treg cells interacts with CD80 and CD86 on antigen-presenting cells (APCs), which results in the inhibition of antigen presentation and maturation functions of APCs.[50] Furthermore, the activation of indoleamine 2,3-dioxygenase (IDO) expressed in DCs ultimately leads to the suppression of Teffs.[51] PD-1 binds to its ligand PD-L1 and PD-L2 on DCs, which gives rise to the inhibition of Teffs via enhancing the transactivation of Smad3 by TGF-β.[52] Binding of lymphocyte activation gene 3 (LAG-3) to major histocompatibility complex class II (MHC-II) molecules expressed on immature DCs induces inhibitory signaling pathways which suppresses DCs maturation and the activation of Teffs.[53] Caspase-8 activated by the combination of tumor necrosis factor (TNF)–related apoptosis-inducing ligand (TRAIL) and death receptor 5 (DR5) induces apoptosis in effector lymphocytes.[54,55] CD25, also known as interleukin IL-2 receptor (IL-2R), has been demonstrated to control the acquisition of cytotoxic activity of $CD4^+$T cells by competing for IL-2.[56]

In addition to the molecules mentioned above, Treg cells exert their immunosuppressive functions through soluble intermediates. New evidence emphasizes the significance of adenosine and cAMP in the ability of Treg cells to inhibit Teffs.[57,58] Ectoenzymes CD39 and CD73 expressed on Treg cells were shown to raise the concentration of adenosine, which suppressed the function of Teffs through activating the adenosine A2A receptor.[59,60] Granzyme-A, granzyme-B

and perforin ensure the cytolysis of Treg cells to other immune cells, such as B cells, NK cells and $CD8^+$ T cells.[61–64] Anti-inflammatory cytokines, such as IL-10, TGF-β and IL-35, mediate the anti-inflammatory effect of Treg cells.[65]

The Relationship with Pregnancy

The Origin of Decidual Treg Cells

Decidual Treg cells originate from peripheral blood Treg cells, including tTreg cells and pTreg cells, exhibiting varying phenotypic heterogeneity according to the cycle and environment.[27,66,67] Recruitment of Treg cells into the uterus commences in endometrial proliferation stage of each cycle and peaks at ovulation.[68] Estrogen in uterine and TGF-β and prostaglandin (PGE) in seminal fluid play a role in recruiting macrophages and DCs, which makes them acquire M2 macrophages and tolerogenic DCs (tDCs) phenotypes. Interferon-gamma (IFN-γ) and IL-10 secreted by uterine natural killer (uNK) cells, Granulocyte-macrophage CSF (GM-CSF) and chemokines secreted by uterine epithelial cells also facilitate the acquirement of M2 macrophages and tDC phenotypes.[69,70] tDCs take up paternal alloantigens in seminal fluid and present antigen to Th0 cells in uterus-draining para-aortic lymph nodes (PALNs).[71,72] Later, Th0 cells can be activated and differentiated into pTreg cells. In mice, systemic expansion and accumulation of tTreg cells in the PALNs and uterus occur during the estrous stage in response to elevated levels of estradiol (E2) at ovulation.[73] During and before embryo implantation, pTreg and tTreg cells are recruited to the uterus and retained there. Treg cells increased in the early and middle trimesters and decreased prior to delivery, which is the similar pattern as Treg cells in peripheral blood.[74]

Regulating Trophoblasts Invasion and Uterine Spiral Artery Remodeling

Embryo implantation necessitates trophoblast infiltration and remodeling of the uterine spiral arteries (SpA). During embryo implantation priming, the excessive production of IL-2 and IFN-γ enhances the development of cytotoxic $CD8^+$ T cells, which subsequently contribute to fetal loss.[75] Meanwhile, unrestrained Teffs release inflammatory cytokines and play cytotoxicity effect on trophoblast through antigen-dependent, which adversely affects placental development.[75,76] Decidual Treg cells may contribute to constraining Teffs in early pregnancy by expressing CTLA4, CD25, and PD-L1, and secreting TGF-β as well as IL-10.[77,78]

A variety of immune cells play a synergistic role in the embryo implantation, such as uNK cells, uterine dendritic cells (uDC) and uterine mast cells (uMC).[79–81] Treg cells cooperate with them to support the formation of decidua and promote embryo implantation.[59] M2 macrophages, tDC and uNK cells promote the peripheral differentiation of Treg cells and recruitment to the uterus.[69,70] On the one hand, Treg cells respond to epithelial cell-derived chemokine C-C motif ligand (CCL) 3, CCL4, CCL5, and CCL19.[82,83] Meanwhile, they inhibit the activation and function of Th1 and Th17 cells by consuming IL-2 or other inhibitory mechanisms.[77,78,84] On the other hand, Treg cells control inflammation by releasing TGF-β, IL-10 and heme oxygenase-1 (HO-1) to interact with DCs and uNK cells.[77,78,85] This eventually facilitated decidualization and embryo implantation.[51,85–88] Besides, the regulatory loop between trophoblasts and maternal immune cell subsets might be bidirectional. An interesting finding suggests that trophoblasts regulated the differentiation of maternal $CD4^+$T cells into immunosuppressive Treg cells, while $CD4^+$T cells might promote the growth and invasiveness of trophoblasts.[89]

In recent years, increasing evidence has shown that Treg cells play an important role in the vascular endothelium and blood flow homeostasis.[13,14] uNK cells regulate the invasion of extravillous trophoblasts as well as displacement of endothelial cells and smooth muscle cells (SMCs) by releasing IFN-γ, which ultimately facilitates the decidual vascular remodeling.[81,90,91] Treg cells suppress inflammatory activation and modulate the phenotypes of decidual uNK cells, macrophages and DCs by releasing TGF-β, IL-10 and HO-1, which promotes the decidual vascular remodeling.[16,77,78,85] Treg cells restrict the activation and infiltration of M1 macrophages, so as to reduce the release of tumor necrosis factor α (TNF-α) and improve the vascular endothelial microenvironment.[13,14] At the same time, they inhibit the erosive effect of Th1 and Th17 on blood vessels,[12,78] which gives rise to diminished vascular resistance and increased blood supply to the placenta (Figure 1).

The Phenotypes of Decidual Treg Cells

The Treg cell population during pregnancy exhibits remarkable diversity, both in the peripheral blood and at the maternal–fetal interface.[9] Until now, the populations of Treg cells at the maternal–fetal interface and their contribution

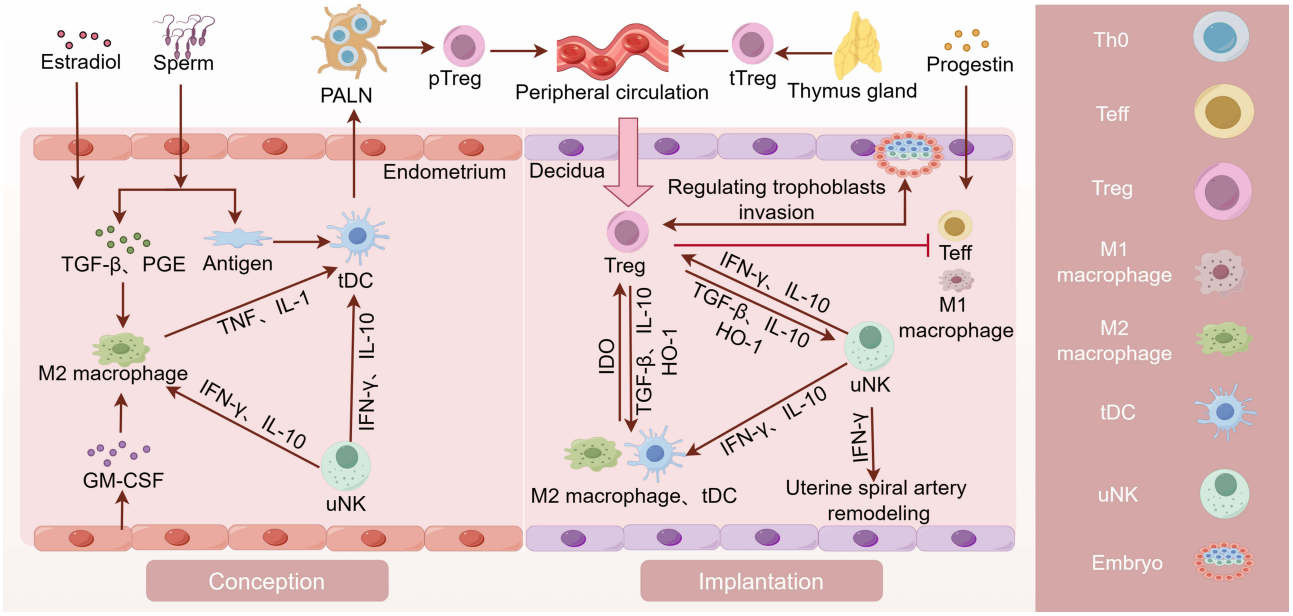

Figure 1 Mechanisms of Treg Cells in Female Pregnancy. Estrogen and semen recruit macrophages and DCs, which promotes their polarization towards M2 macrophages and tDC phenotypes. tDCs uptake paternal antigens in semen and transport them to the PALN draining the uterus. Under the stimulation of paternal antigens, Th0 cells in PALN differentiate into pTreg cells. pTreg cells and tTreg cells converge in the peripheral circulation and re-enter the uterine cavity during the implantation stage to exert their functions. Decidual Treg cells restrict Teffs by secreting IL-10 and TGF-β and expressing CD25, CTLA4 and PD-L1, which directly promotes the embryo implantation. Additionally, they work in collaboration with decidual immune cells to promote decidualization and enhance endometrial receptivity. Treg cells not only directly inhibit Teffs and M1 macrophages, but also work in collaboration with M2 macrophages, uNK, and tDC cells to promote trophoblast invasion and vascular remodeling. PALN, para-aortic lymph node. (By Figdraw).

to the decidual microenvironment have not been fully defined. Originally, a population of $CD4^+CD25^+$ T cells, expressing intracellular CTLA-4, glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) and OX40 (CD134), was identified in the human decidua.[92] It is implied that Treg cells exist in decidua and play an important role in the regulation of local maternal tolerance towards the fetus.[92] Later, Dimova firstly demonstrated the presence and in situ distribution of $CD4^+$ $Foxp3^+$ cells in decidua,[93] which were classified into $CD4^+$ $CD25^{++}$ $Foxp3^+$, $CD4^+$ $CD25^+$ $Foxp3^+$, and $CD4^+$ $CD25^-$ $Foxp3^+$ subpopulations on the basis of CD25 expression.[93] These Foxp3+ cells were found to express TGFβ1 mRNA and exhibit surface molecules consistent with Treg phenotype, including CD45RO (a marker for memory lymphocytes), CTLA-4, CD103, Nrp-1, LAG-3, and CD62L.[93]

Recently, three distinct types of decidual $CD4^+$ Treg cells in healthy pregnancies were investigated, whose phenotypes are $CD25^{HI}$ $FoxP3^+$, $PD1^{HI}$ $FoxP3^-$ $IL\text{-}10^+$ and $TIGIT^+$ $FoxP3^{dim}$ Treg cells.[94] The characteristics of these three types of Treg cells are summarized in Table 1. In comparison to Treg cells in the blood, $CD25^{HI}FoxP3^+$ Treg cells in the decidual tissue exhibit higher levels of co-inhibitory proteins or mRNAs, such as CTLA-4, GITR, CD39, ST2, and LRRC32.[94] This observation indicates an enhanced activation and suppressive function of Treg cells in the decidual tissue, which plays a crucial role in regulating inflammation at the maternal–fetal interface.

Unlike the studies above, a systematic review discussed the heterogeneity within the $FoxP3^-$ Treg cell compartment and their role in pregnancy.[9] $FoxP3^-HLA\text{-}G^+$Treg cells have been identified in both decidua and peripheral blood during pregnancy, which plays a crucial role in establishing a tolerogenic decidual microenvironment by secreting IL-10 and soluble HLA-G.[95–97] Tr1 Treg cells, which primarily product IL-10[98–100] and express co-signaling molecules such as PD-1, CTLA-4, TIM-3, ICOS, GARP (LRRC32), and latency associated peptide (LAP),[101–103] are also found in both peripheral blood and human decidua.[94,104] Additionally, the observation of mRNA cytokine profiles similar to Th3 represents the first description of a potential presence of Th3 cells in the decidua.[93] The main suppressive effects of Th3 Treg cells are mediated by TGF-β in a cell-contact independent manner[105,106] (Table 1).

Table 1 Different Phenotypes of Treg Cells During Pregnancy

Phenotypes	Characteristics	Function	References
$CD25^{HI}FoxP3^{+}$	High expression of CD25, FoxP3 and Helios; the lack of CD45RA and CD127	Production of the lowest level of IL-10, IFN-γ and IL- 2; suppression of IFN-γ and TNF-α secreted by $CD4^{+}$ and $CD8^{+}$Teffs	[90]
$PD1^{HI}FoxP3^{-}IL\text{-}10^{+}$	High expression of PD-1; the lack of FoxP3 and Helios; low CD25	Generation of the highest level of IL-10 and IFN-γ; suppression of proliferation of $CD4^{+}$ (but not $CD8^{+}$) Teffs in an IL-10-dependent manner	[90]
$TIGIT^{+}FoxP3^{dim}$	High levels of TIGIT; low levels of FoxP3, Helios, PD-1 and CD25	Expression of the high levels of IFN-γ and IL-2 and low levels of IL-10; inhibition of $CD4^{+}$Teffs proliferation	[90]
$FoxP3^{-}HLA\text{-}G^{+}$	Secretion of sHLA-G and IL-10; cell interaction with HLA-G	The reduced killing capacity of T cells and NK cells; induction of the tolerant macrophages and DC cells	[91–93]
Tr1	Express CD49b, LAG-3, PD-1, CTLA-4, TIM-3, ICOS, GARP and LAP; produce IL-10 and TGF-β; low levels of IFN-γ, IL-5, IL-2, and granzyme B; KIR receptors, ectoenzymes CD39 and CD73	Suppression of T cell proliferation and in favor of creating the tolerogenic decidual microenvironment; inhibition of other immune cells (such as DC and Mφ)	[90,94–100]
Th3	Express Helios, LAP and GARP; secretion of TGF-β and IL-10	Induction of DC-10s and Treg cells by IL-10; inhibition of NK cells and T cells and APC by TGF-β	[89,101,102]

Abbreviations: FoxP3, Forkhead box P3; IL-2,10, Interleukin-2,10; IFN-γ, Interferon-gamma; TNF-α, The TNF-related apoptosis-inducing ligand; PD-1, Programmed death-1 ligand; Teffs, Effector T cells; TIGIT, The ITIM domain protein; HLA-G, Human Leukocyte Antigen G; sHLA-G, soluble Human Leukocyte Antigen G; NK, natural killer; DC, Dendritic; Mφ, macrophages; APC, Antigen-presenting cell, TGF-β, Transforming growth factor beta; LAG-3, Lymphocyte activation gene 3; CTLA-4, Cytotoxic T lymphocyte associated antigen-4, TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; ICOS, Inducible co-stimulator; LAP, Latency associated peptide.

The Relationship with URSA

$CD4^{+}$ $CD25^{+}$ Treg-deficient mouse model was established to demonstrate that allogeneic fetuses are consistently rejected without Treg cells.[107] Transferring of Treg cells into mice prone to miscarriage resulted in an increase number of uMC, which possess a positive impact on the remodeling of the placenta and SpA.[108] Both in the peripheral blood and decidua, the number and function of Treg cells are diminished in women experiencing recurrent pregnancy loss (RPL), when compared to women in control group.[109] This evidence confirmed that insufficient Treg numbers or inadequate function were implicated in RSA.[10] The following is the main hypothesis of the relationship between Treg cells and URSA.

Systemic Immune Imbalance

A number of scholars have analyzed the endometrial cytokine profile in normal female and patients with recurrent abortion. The luteal-phase endometrium of patients with URSA exhibited increased expression of the inflammatory mediators, such as TNF-α, IL-1β and IFN-γ.[110,111] At the same time, the levels of TGF-β, IL-4, IL-10, leukemia inhibitory factor (LIF), and vascular endothelial growth factor (VEGF) were reduced in the endometrium of URSA patients during the luteal phase.[110,111] In addition, several studies demonstrated that the endometrium of women with URSA was accompanied by the alteration of uNK cells and reduced expression of key angiogenic regulators.[112–115] TGF-β and IL-10 secreted by Treg cells were not only involved in immune regulation but also directly benefited the vasculature at the maternal–fetal interface.[116] The increased level of TGF-β1 in serum may lead to a reduction in the abortion rate in a mouse model prone to miscarriage.[117] Overall, this evidence indicates that the embryo may not survive in the inflammatory stage of implantation due to the failure to transition to an anti-inflammatory and proangiogenic immune environment. These dysfunctions may be associated with reduced numbers of Treg cells and the increase of Th17, Th1 and M1 macrophages in decidua and peripheral blood.[118–123]

Phenotypic Plasticity and Lineage Stability

Cytokines, hormones, micro-RNAs, the reproductive tract microbiome, and seminal fluid composition all have the potential to interfere with the response of Treg cells,[124–127] because the newly generated pTreg cells are susceptible to lineage instability and phenotype switching.[128] $CD4^{+}$ T cells from patients with RM were cultured with DCs and the partner's seminal fluid antigens, which suggested that $CD4^{+}IL\text{-}17^{+}$and $CD4^{+}IFN\text{-}\gamma^{+}$cells proliferated excessively.[129] At

the same time, the study revealed that fewer $CD4^+CD25^+FoxP3^+$ Treg cells were generated by patients with RM compared with fertile controls.[129] High levels of IFN-γ could skew Th0 differentiation toward Th17 cells and caused Treg cells to transdifferentiate.[130,131] In addition, deficiency in IL-10 triggers an unstable Treg response in the decidua, resulting in a quicker conversion of phenotypes and impairing ability to effectively anti-inflammation during the later stages of pregnancy.[132,133] There remains a highly contentious topic: pTreg cells shift the phenotypes and express cytokines that are characteristic of Teff lineages within hyperinflammatory environment.[128,131] Treg cells undergoing trans-differentiation into Th1 or Th17 cells were known as exTreg cells, which promote inflammation and other immune responses.[128] The phenotypic plasticity and switching abilities of Treg cells may contribute to the maternal ability to invest differently in reproductive opportunities. In normal circumstances, Treg cells maximize the maternal decidual receptivity and offspring adaptability by interacting with the environment, hormones, and cells.[126,128,134] However, there is also study showing that excessive immune adaptation during pregnancy might predispose pregnant females to the susceptibility of viral infections.[135] The ability of Treg cells to transdifferentiate into Teffs under conditions of severe infection, excessive inflammation, or disruption of fetal development allows for the termination of pregnancy to preserve maternal survival.[136]

Recently, evidence has focused on immune checkpoint molecules and stability markers of Treg cells, such as Foxp3, Helios, Nrp-1, ICOS, PD-1, TIGIT and TIM-3, which is aimed to explain the stability of inhibitory function of Treg cells.[23–27] The signature of endometrial Treg transcriptomic was identified.[118] The researchers observed increased expression of sphingosine-1-phosphate receptor 1 (S1PR1) and decreased levels of TIGIT protein in women with primary URSA, which suggested reduced inhibitory capacity of Treg cells in women with primary URSA.[118] In addition, Hu et al discovered that $Tim3^+$ Treg cells constituted over 60% Treg cells in the mouse decidua during early pregnancy.[8] Meanwhile, they observed the significantly lower Tim-3 expression on Treg cells in URSA, indicating that decreased $Tim\text{-}3^+$ Treg cells might have a close relationship with impaired immunologic tolerance in women suffering URSA.[8] In addition, Treg cells from women with RM exhibited fewer $CD45RA^-$ cells and reduced expression of CTLA4 and Ubc13(an ubiquitin E2 conjugating enzyme),[66] which implied that the stability of Treg cells was reduced in URSA[120,129,137] (Figure 2).

Therapeutic Prospects for Targeting Treg Cells

Reproductive disorders caused by instability or insufficient production of Treg cells pose a challenging problem to be addressed, which may be the result of multiple factors in the biological evolution process.[27,66,134,138] Interventions aimed at increasing the number and improving the function of Treg cells are currently being developed and are showing promise in the treatment of tissue transplantation and autoimmune diseases. With the rapid progress in Treg cell therapeutics, there is a great potential for targeting Treg cells to address URSA.[139] Here, we propose three points:

Signaling of Treg Cells and Stability

In recent years, some scientists have proposed promoting the stability of Treg cells through selective gene knockout. However, the safety concerns associated with this approach must be taken into consideration. For example, IL-6 triggers the signal transducer and activator of transcription 3 (STAT3) transduction pathway, which then induces the expression of the DNA methyltransferase 1 (DNMT1).[140,141] This leads to the methylation and subsequent downregulation of the Foxp3 site, ultimately resulting in the development of naive T cells into Th17 cells.[142] Therefore, targeting IL-6 receptor (IL-6R) or STAT3 in Treg cells could be a viable strategy to enhance the stability of Treg cells and protect them from alterations caused by IL-6 signaling.[143] In human, IL-6R-targeted antibodies have been identified as a potential therapeutic approach for inflammatory and autoimmune diseases like RA, Crohn's disease, and systemic lupus erythematosus (SLE).[144–146]

IL-2 plays a crucial role in the generation, survival, stability, and function of Treg cells.[147] In the absence of IL-2, Treg cells undergo apoptotic death, which leads to autoimmunity.[148] Therefore, various strategies have been developed to utilize IL-2 as a therapeutic pathway to improve the stability, effectiveness and survival of Treg cells in vivo.[147,149] The hypothesis suggests that administering low doses of IL-2 would primarily activate Treg cells and restrict the activation of Teffs, which is contrary to the impact of high doses of IL-2.[150–153] Two therapeutic strategies targeting IL-2 have primarily been developed, and IL-2 low-dose therapy and monoclonal antibodies that target IL-2. F5111.2, a fully human

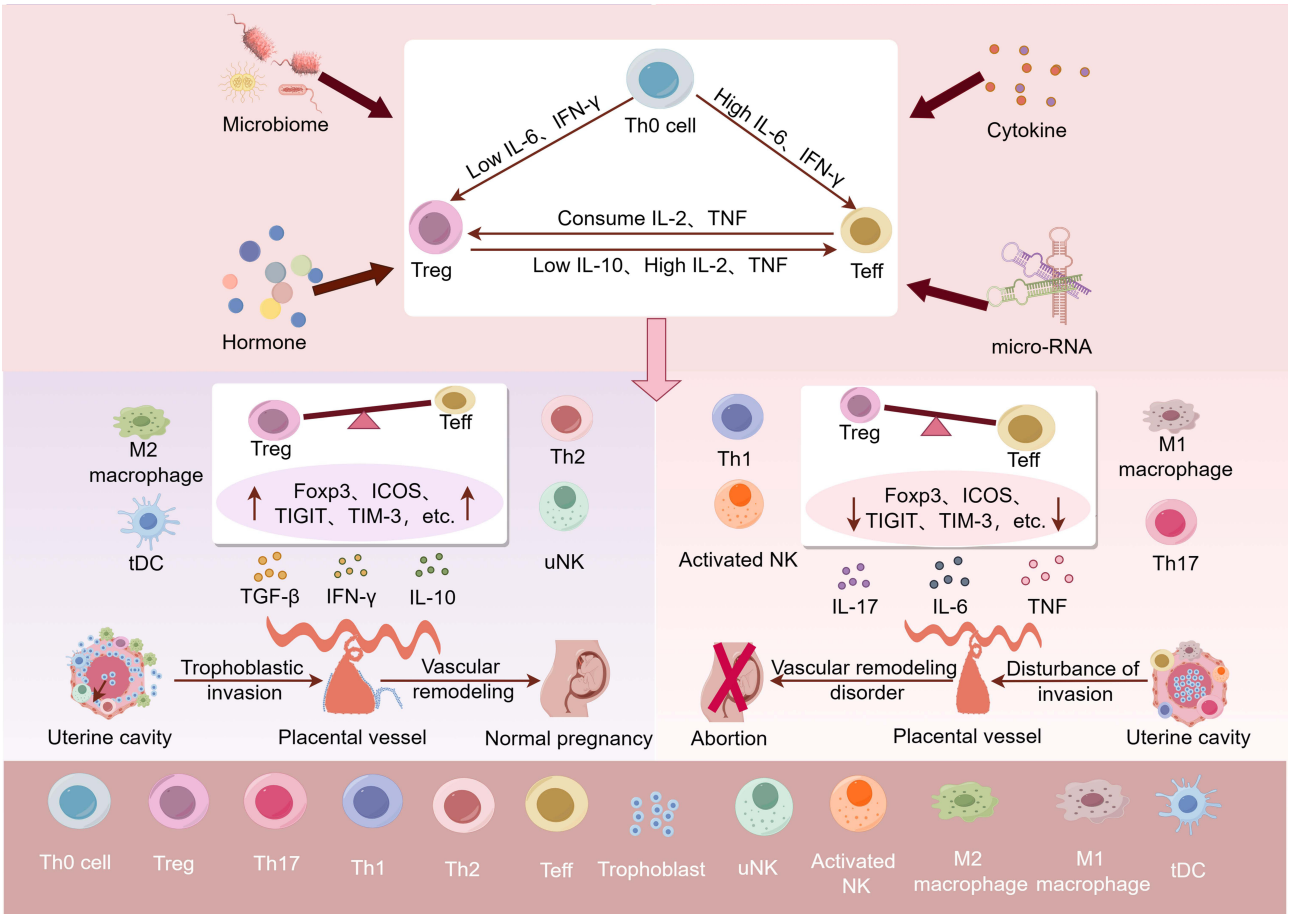

Figure 2 The relationship between Decidual Treg cells and URSA. In human, cytokines, hormones, micro-RNAs, the reproductive tract microbiome, and seminal fluid composition all have the potential to interfere with the immune balance at the maternal–fetal interface. High levels of IL-6 and IFN-γ could skew Th0 differentiation toward Teffs and cause Treg cells to transdifferentiate. Newly generated pTreg cells are susceptible to lineage instability and phenotype switching. High levels of IL-2, TNF and low levels of IL-10 could skew pTreg cells differentiation toward Teffs. If pTreg cells express additional markers associated with functional stability, such as Foxp3, ICOS, TIGIT, and TIM3, it could potentially shift the immune balance at the maternal–fetal interface towards immune tolerance. This may lead to elevated TGF-β, IL-10, M2 macrophages and tDC cells, which promotes trophoblast invasion, vascular remodeling and placental development. Conversely, if the newly generated pTreg cells are unstable, it could shift the immune balance at the maternal–fetal interface towards pro-inflammation. This could result in elevated IL-6, IL-17, TNF, M1 macrophages, Th1 cells and etc, which may hinder trophoblast invasion, vascular remodeling, and ultimately causing placental dysplasia and URSA. (By Figdraw).

anti-IL-2 antibody, were recently developed to induce the preferential expansion of human Treg cells by blocking IL-2Rβ and reducing IL-2Rα.[152]

Interventions to Increase Treg Cell Numbers

The decrease in number of Treg cells in the decidua of women with URSA is likely a consequence of impaired generation or recruitment of Treg cells during pregnancy establishment,[118,154] which suggests that Treg cells possess therapeutic potential in women with URSA.[155] Co-expression of a chemokine receptor, which could identify chemokines in an inflammatory environment, may improve Treg cell functionality.[143] In related studies, overexpression of chemokine receptors has been found to improve chimeric antigen receptor (CAR) T cells homing to the tumor, resulting in enhanced antitumor activity and improved survival.[156–158] A recent study elucidated that histone methyltransferase Nsd2 upregulated the expression of C-X-C chemokine receptor type 4 (CXCR4) through the H3K36me2 modification, which plays a crucial role in promoting the recruitment of Treg cells into the decidua and ultimately improved pregnancy outcomes in mice.[159]

In addition to the methods of increasing number of Treg cells endogenously, methods of artificially supplementing Treg cells have been developed. The method of adoptive transplantation of Treg cells to improve the prognosis of spontaneous abortion has demonstrated effectiveness in mouse models and is anticipated to be a promising immunological treatment for women with URSA.[155] Evidence suggests that Treg cells from umbilical cord blood display higher repertoire diversity and

lineage stability compared to those from adult peripheral blood, providing a feasible basis for Treg cell therapy.[160] Before the development of endogenous Treg cells from a donor's bone marrow cells, using cord blood-derived Treg cells could offer a temporary solution.[143]

Behavioral and Pharmacological Interventions in URSA

Metabolic, autoimmune conditions, inflammatory exposures and age strongly affect the immune response.[139,161–163] Metabolic imbalance, such as hyperglycemia and insulin resistance, will skew the energy source driving the T cell pool, which eventually results in an increased number of Th17 cells and declined in the number of Treg cells.[164] Microbiome disorders, deficiencies in micronutrients and vitamins have a specific impact on Treg cells. Treating these disorders and deficiencies is anticipated to enhance uterine immune function,[165] which may improve the prognosis of URSA in turn.

Besides, preexisting health conditions and lifestyle factors are also significant in male partners, because of the affection of seminal fluid quality and healthy female response.[166] Incompatibility or insufficient disparity of HLA between partners may lead to low immunogenicity of male alloantigens, leading to either excessive inhibition or activation of uNK cells or hindering the priming and expansion of the Treg cell population.[167] Providing guidance on seminal fluid priming during preconception planning may be a promising approach for nulliparous women without known compatibility issues.[167] More interestingly, exercise and sunlight exposure potentially increase Treg cells by regulating their homeostasis.[168,169] Intravenous immunoglobulin, prednisolone, and TNF inhibitors, initially developed for other autoinflammatory or specific autoimmune diseases,[61,170–172] have been investigated in patients with URSA and recurrent implantation failure. However, the clinical data supporting efficacy are limited.[173] Progesterone has been shown to effectively inhibit the generation of Th1 and Th17 cells while also inducing Treg cell differentiation.[61,174–176]

Conclusion and Prospects

The combination of animal models and clinical studies provide evidence that decidual Treg cells play a role in reducing inflammation during the early pregnancy. They also contribute to creating an environment in the decidua that supports implantation receptivity and placenta formation. Immune maladaptation or imbalance leading to instability or insufficient of Treg cells, which may be a cause of URSA. A large number of studies should be devoted to investigate the subsets of Treg cells, which can gain more insights into their functions and roles in URSA. It is necessary to continually explore ways to improve the number and stability of Treg cells, which may be a therapeutic target for URSA.

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Disclosure

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References

1. Förster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. *Nat Rev Immunol*. 2008;8(5):362–371. doi:10.1038/nri2297
2. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. *Annu Rev Immunol*. 2020;38:541–566. doi:10.1146/annurev-immunol-042718-041717
3. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008;133:775–787. doi:10.1016/j.cell.2008.05.009
4. Jiang Q, Yang G, Liu Q, Wang S, Cui D. Function and Role of Regulatory T Cells in Rheumatoid Arthritis. *Front Immunol*. 2021;12:626193. doi:10.3389/fimmu.2021.626193
5. Turner JA, Stephen-Victor E, Wang S, et al.. Regulatory T Cell-Derived TGF-β1 controls multiple checkpoints governing allergy and autoimmunity. *Immunity*. 2020;53:1202–1214.e6. doi:10.1016/j.immuni.2020.10.002
6. Bettini M, Bettini ML. Function, Failure, and the Future Potential of Tregs in Type 1 Diabetes. *Diabetes*. 2021;70:1211–1219. doi:10.2337/dbi18-0058
7. Daenthanasanmak A, Iamsawat S, Chakraborty P, et al.. Targeting Sirt-1 controls GVHD by inhibiting T-cell allo-response and promoting Treg stability in mice. *Blood*. 2019;133:266–279. doi:10.1182/blood-2018-07-863233

8. Hu X, Zhu Q, Wang Y, et al.. Newly characterized decidual Tim-3+ Treg cells are abundant during early pregnancy and driven by IL-27 coordinately with Gal-9 from trophoblasts. *Hum Reprod*. 2020;35:2454–2466. doi:10.1093/humrep/deaa223
9. Krop J, Heidt S, Claas F, Eikmans M. Regulatory T Cells in Pregnancy: it Is Not All About FoxP3. *Front Immunol*. 2020;11:1182. doi:10.3389/fimmu.2020.01182
10. Robertson SA, Care AS, Moldenhauer LM. Regulatory T cells in embryo implantation and the immune response to pregnancy. *J Clin Invest*. 2018;128:4224–4235. doi:10.1172/JCI122182
11. Care AS, Bourque SL, Morton JS, Hjartarson EP, Robertson SA, Davidge ST. Reduction in regulatory T cells in early pregnancy causes uterine artery dysfunction in mice. *Hypertension*. 2018;72:177–187. doi:10.1161/HYPERTENSIONAHA.118.10858
12. Samstein RM, Josefowicz SZ, Arvey A, Treuting PM, Rudensky AY. Extrathymic generation of regulatory T cells in placental mammals mitigates maternal-fetal conflict. *Cell*. 2012;150:29–38. doi:10.1016/j.cell.2012.05.031
13. Tamosiuniene R, Manouvakhova O, Mesange P, et al.. Dominant role for regulatory T cells in protecting females against pulmonary hypertension. *Circ Res*. 2018;122:1689–1702. doi:10.1161/CIRCRESAHA.117.312058
14. Sharma M, Schlegel MP, Afonso MS, et al.. Regulatory T cells license macrophage pro-resolving functions during atherosclerosis regression. *Circ Res*. 2020;127:335–353. doi:10.1161/CIRCRESAHA.119.316461
15. Williams PJ, Searle RF, Robson SC, Innes BA, Bulmer JN. Decidual leucocyte populations in early to late gestation normal human pregnancy. *J Reprod Immunol*. 2009;82:24–31. doi:10.1016/j.jri.2009.08.001
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. *Biol Reprod*. 2010;82:698–705. doi:10.1095/biolreprod.109.081208
17. Tilburgs T, Roelen DL, van der Mast BJ, et al.. Differential distribution of CD4(+)CD25(bright) and CD8(+)CD28(-) T-cells in decidua and maternal blood during human pregnancy. *Placenta*. 2006;27:S47–53. doi:10.1016/j.placenta.2005.11.008
18. Sakaguchi S. Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol*. 2004;22:531–562. doi:10.1146/annurev.immunol.21.120601.141122
19. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol*. 1995;155:1151–1164. doi:10.4049/jimmunol.155.3.1151
20. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science*. 2003;299:1057–1061. doi:10.1126/science.1079490
21. Khattri R, Cox T, Yasayko SA, Ramsdell F. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol*. 2003;4:337–342. doi:10.1038/ni909
22. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol*. 2003;4:330–336. doi:10.1038/ni904
23. Zhang YH, Sun HX. Immune checkpoint molecules in pregnancy: focus on regulatory T cells. *Eur J Immunol*. 2020;50:160–169. doi:10.1002/eji.201948382
24. Miko E, Meggyes M, Doba K, Barakonyi A, Szereday L. Immune Checkpoint Molecules in Reproductive Immunology. *Front Immunol*. 2019;10:846. doi:10.3389/fimmu.2019.00846
25. Xu YY, Wang SC, Li DJ, Du MR. Co-signaling molecules in maternal-fetal immunity. *Trends Mol Med*. 2017;23:46–58. doi:10.1016/j.molmed.2016.11.001
26. Joller N, Kuchroo VK. Tim-3, Lag-3, and TIGIT. *Curr Top Microbiol Immunol*. 2017;410:127–156. doi:10.1007/82_2017_62
27. Wagner MI, Jöst M, Spratte J, et al.. Differentiation of ICOS+ and ICOS- recent thymic emigrant regulatory T cells (RTE T regs) during normal pregnancy, pre-eclampsia and HELLP syndrome. *Clin Exp Immunol*. 2016;183:129–142. doi:10.1111/cei.12693
28. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2020;113:533–535. doi:10.1016/j.fertnstert.2019.11.025
29. Dimitriadis E, Menkhorst E, Saito S, Kutteh WH, Brosens JJ. Recurrent pregnancy loss. *Nat Rev Dis Primers*. 2020;6:98. doi:10.1038/s41572-020-00228-z
30. Garrido-Gimenez C, Alijotas-Reig J. Recurrent miscarriage: causes, evaluation and management. *Postgrad Med J*. 2015;91:151–162. doi:10.1136/postgradmedj-2014-132672
31. Alves C, Jenkins SM, Rapp A. *StatPearls*. Treasure Island (FL): StatPearls; 2024.
32. Daumová M, Hadravská Š, Putzová M. Spontaneous abortion in the first trimester of pregnancy. *Cesk Patol*. 2023;59(2):60–63.
33. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2012;98:1103–1111. doi:10.1016/j.fertnstert.2012.06.048
34. Sun H, Mao J, Su X, Du Q. Impact of spontaneous abortion history and induced abortion history on perinatal outcomes of singleton pregnancies. *BMC Public Health*. 2023;23(1):2360. doi:10.1186/s12889-023-17264-5
35. de Ziegler D, Frydman RF. Recurrent pregnancy losses, a lasting cause of infertility. *Fertil Steril*. 2021;115(3):531–532. doi:10.1016/j.fertnstert.2020.12.004
36. Schatz F, Guzeloglu-Kayisli O, Arlier S, Kayisli UA, Lockwood CJ. The role of decidual cells in uterine hemostasis, menstruation, inflammation, adverse pregnancy outcomes and abnormal uterine bleeding. *Hum Reprod Update*. 2016;22:497–515. doi:10.1093/humupd/dmw004
37. Du Y, Fang Q, Zheng SG. Regulatory T cells: concept, classification, phenotype, and biological characteristics. *Adv Exp Med Biol*. 2021;1278:1–31. doi:10.1007/978-981-15-6407-9_1
38. Josefowicz SZ, Niec RE, Kim HY, et al.. Extrathymically generated regulatory T cells control mucosal TH2 inflammation. *Nature*. 2012;482:395–399. doi:10.1038/nature10772
39. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. *Annu Rev Immunol*. 2012;30:531–564. doi:10.1146/annurev.immunol.25.022106.141623
40. Abbas AK, Benoist C, Bluestone JA, et al.. Regulatory T cells: recommendations to simplify the nomenclature. *Nat Immunol*. 2013;14:307–308. doi:10.1038/ni.2554
41. Smigiel KS, Srivastava S, Stolley JM, Campbell DJ. Regulatory T-cell homeostasis: steady-state maintenance and modulation during inflammation. *Immunol Rev*. 2014;259:40–59. doi:10.1111/imr.12170

42. Liston A, Gray DH. Homeostatic control of regulatory T cell diversity. *Nat Rev Immunol*. 2014;14:154–165. doi:10.1038/nri3605
43. Dias S, D'Amico A, Cretney E, et al.. Effector Regulatory T cell differentiation and immune homeostasis depend on the transcription factor Myb. *Immunity*. 2017;46:78–91. doi:10.1016/j.immuni.2016.12.017
44. Burzyn D, Benoist C, Mathis D. Regulatory T cells in nonlymphoid tissues. *Nat Immunol*. 2013;14:1007–1013. doi:10.1038/ni.2683
45. Miragaia RJ, Gomes T, Chomka A, et al.. Single-cell transcriptomics of regulatory T cells reveals trajectories of tissue adaptation. *Immunity*. 2019;50:493–504.e7. doi:10.1016/j.immuni.2019.01.001
46. Yu X, Harden K, Gonzalez LC, et al.. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat Immunol*. 2009;10:48–57. doi:10.1038/ni.1674
47. Brlić P K, Lenac Roviš T, Cinamon G, Tsukerman P, Mandelboim O, Jonjić S. Targeting PVR (CD155) and its receptors in anti-tumor therapy. *Cell Mol Immunol*. 2019;16:40–52. doi:10.1038/s41423-018-0168-y
48. Joller N, Lozano E, Burkett PR, et al.. Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. *Immunity*. 2014;40:569–581. doi:10.1016/j.immuni.2014.02.012
49. Levine AG, Mendoza A, Hemmers S, et al.. Stability and function of regulatory T cells expressing the transcription factor T-bet. *Nature*. 2017;546:421–425. doi:10.1038/nature22360
50. Paust S, Lu L, McCarty N, Cantor H. Engagement of B7 on effector T cells by regulatory T cells prevents autoimmune disease. *Proc Natl Acad Sci USA*. 2004;101:10398–10403. doi:10.1073/pnas.0403342101
51. Fallarino F, Grohmann U, Hwang KW, et al.. Modulation of tryptophan catabolism by regulatory T cells. *Nat Immunol*. 2003;4:1206–1212. doi:10.1038/ni1003
52. Tan CL, Kuchroo JR, Sage PT, et al.. PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. *J Exp Med*. 2021;218:e20182232.
53. Maruhashi T, Sugiura D, Okazaki IM, et al.. Binding of LAG-3 to stable peptide-MHC class II limits T cell function and suppresses autoimmunity and anti-cancer immunity. *Immunity*. 2022;55:912–924.e8. doi:10.1016/j.immuni.2022.03.013
54. Bodmer JL, Holler N, Reynard S, et al.. TRAIL receptor-2 signals apoptosis through FADD and caspase-8. *Nat Cell Biol*. 2000;2:241–243. doi:10.1038/35008667
55. Ren X, Ye F, Jiang Z, Chu Y, Xiong S, Wang Y. Involvement of cellular death in TRAIL/DR5-dependent suppression induced by CD4(+)CD25(+) regulatory T cells. *Cell Death Differ*. 2007;14:2076–2084. doi:10.1038/sj.cdd.4402220
56. Śledzińska A, Vila de Mucha M, Bergerhoff K, et al.. Regulatory T Cells Restrain Interleukin-2- and Blimp-1-Dependent Acquisition of Cytotoxic Function by CD4(+) T Cells. *Immunity*. 2020;52:151–166.e6. doi:10.1016/j.immuni.2019.12.007
57. Sundström P, Stenstad H, Langenes V, et al.. Regulatory T cells from colon cancer patients inhibit effector T-cell migration through an adenosine-dependent mechanism. *Cancer Immunol Res*. 2016;4:183–193. doi:10.1158/2326-6066.CIR-15-0050
58. Klein M, Bopp T. Cyclic AMP represents a crucial component of treg cell-mediated immune regulation. *Front Immunol*. 2016;7:315. doi:10.3389/fimmu.2016.00315
59. Su W, Chen X, Zhu W, et al.. The cAMP-adenosine feedback loop maintains the suppressive function of regulatory T cells. *J Immunol*. 2019;203:1436–1446. doi:10.4049/jimmunol.1801306
60. Schneider E, Winzer R, Rissiek A, et al.. CD73-mediated adenosine production by CD8 T cell-derived extracellular vesicles constitutes an intrinsic mechanism of immune suppression. *Nat Commun*. 2021;12:5911. doi:10.1038/s41467-021-26134-w
61. Hayashi Y, Ohnuma K, Furue MK. Pluripotent Stem Cell Heterogeneity. *Adv Exp Med Biol*. 2019;1123:71–94.
62. Zhao DM, Thornton AM, DiPaolo RJ, Shevach EM. Activated CD4+CD25+ T cells selectively kill B lymphocytes. *Blood*. 2006;107:3925–3932. doi:10.1182/blood-2005-11-4502
63. Grossman WJ, Verbsky JW, Barchet W, Colonna M, Atkinson JP, Ley TJ. Human T regulatory cells can use the perforin pathway to cause autologous target cell death. *Immunity*. 2004;21:589–601. doi:10.1016/j.immuni.2004.09.002
64. Gondek DC, Devries V, Nowak EC, et al.. Transplantation survival is maintained by granzyme B+ regulatory cells and adaptive regulatory T cells. *J Immunol*. 2008;181:4752–4760. doi:10.4049/jimmunol.181.7.4752
65. Yano H, Andrews LP, Workman CJ, Vignali D. Intratumoral regulatory T cells: markers, subsets and their impact on anti-tumor immunity. *Immunology*. 2019;157:232–247. doi:10.1111/imm.13067
66. Inada K, Shima T, Ito M, Ushijima A, Saito S. Helios-positive functional regulatory T cells are decreased in decidua of miscarriage cases with normal fetal chromosomal content. *J Reprod Immunol*. 2015;107:10–19. doi:10.1016/j.jri.2014.09.053
67. Hsu P, Santner-Nanan B, Dahlstrom JE, et al.. Altered decidual DC-SIGN+ antigen-presenting cells and impaired regulatory T-cell induction in preeclampsia. *Am J Pathol*. 2012;181:2149–2160. doi:10.1016/j.ajpath.2012.08.032
68. Arruvito L, Sanz M, Banham AH, Fainboim L. Expansion of CD4+CD25+and FOXP3+ regulatory T cells during the follicular phase of the menstrual cycle: implications for human reproduction. *J Immunol*. 2007;178:2572–2578. doi:10.4049/jimmunol.178.4.2572
69. Lee SJ, Song L, Yang MC, et al.. Local administration of granulocyte macrophage colony-stimulating factor induces local accumulation of dendritic cells and antigen-specific CD8+ T cells and enhances dendritic cell cross-presentation. *Vaccine*. 2015;33:1549–1555. doi:10.1016/j.vaccine.2015.02.019
70. Tao Y, Li YH, Zhang D, et al.. Decidual CXCR4(+) CD56(bright) NK cells as a novel NK subset in maternal-foetal immune tolerance to alleviate early pregnancy failure. *Clin Transl Med*. 2021;11:e540.
71. Li Z, Liang X, Chen X, et al.. The role of thymus- and extrathymus-derived regulatory T cells in maternal-fetal tolerance. *Front Immunol*. 2023;14:1109352. doi:10.3389/fimmu.2023.1109352
72. Yasuda I, Shima T, Moriya T, et al.. Dynamic changes in the phenotype of dendritic cells in the uterus and uterine draining lymph nodes after coitus. *Front Immunol*. 2020;11:557720. doi:10.3389/fimmu.2020.557720
73. Kallikourdis M, Betz AG. Periodic accumulation of regulatory T cells in the uterus: preparation for the implantation of a semi-allogeneic fetus. *PLoS One*. 2007;2:e382.
74. Shima T, Sasaki Y, Itoh M, 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;85:121–129. doi:10.1016/j.jri.2010.02.006
75. Moldenhauer LM, Diener KR, Hayball JD, Robertson SA. An immunogenic phenotype in paternal antigen-specific CD8(+) T cells at embryo implantation elicits later fetal loss in mice. *Immunol Cell Biol*. 2017;95:705–715. doi:10.1038/icb.2017.41

76. Chaturvedi V, Ertelt JM, Jiang TT, et al.. CXCR3 blockade protects against Listeria monocytogenes infection-induced fetal wastage. *J Clin Invest*. 2015;125:1713–1725. doi:10.1172/JCI78578
77. Li L, Tu J, Jiang Y, Zhou J, Schust DJ. Regulatory T cells decrease invariant natural killer T cell-mediated pregnancy loss in mice. *Mucosal Immunol*. 2017;10:613–623. doi:10.1038/mi.2016.84
78. Zhang Y, Liu Z, Tian M, et al.. The altered PD-1/PD-L1 pathway delivers the 'one-two punch' effects to promote the Treg/Th17 imbalance in pre-eclampsia. *Cell Mol Immunol*. 2018;15:710–723. doi:10.1038/cmi.2017.70
79. Erlebacher A. Immunology of the maternal-fetal interface. *Annu Rev Immunol*. 2013;31:387–411. doi:10.1146/annurev-immunol-032712-100003
80. Jiang X, Wang H. Macrophage subsets at the maternal-fetal interface. *Cell Mol Immunol*. 2020;17:889–891. doi:10.1038/s41423-020-0435-6
81. Wang F, Qualls AE, Marques-Fernandez L, Colucci F. Biology and pathology of the uterine microenvironment and its natural killer cells. *Cell Mol Immunol*. 2021;18:2101–2113. doi:10.1038/s41423-021-00739-z
82. Guerin LR, Moldenhauer LM, Prins JR, Bromfield JJ, Hayball JD, Robertson SA. Seminal fluid regulates accumulation of FOXP3+ regulatory T cells in the preimplantation mouse uterus through expanding the FOXP3+ cell pool and CCL19-mediated recruitment. *Biol Reprod*. 2011;85:397–408. doi:10.1095/biolreprod.110.088591
83. Shima T, Nakashima A, Yasuda I, et al.. Uterine CD11c+ cells induce the development of paternal antigen-specific Tregs via seminal plasma priming. *J Reprod Immunol*. 2020;141:103165. doi:10.1016/j.jri.2020.103165
84. Blois SM, Ilarregui JM, Tometten M, et al.. A pivotal role for galectin-1 in fetomaternal tolerance. *Nat Med*. 2007;13:1450–1457. doi:10.1038/nm1680
85. Vacca P, Cantoni C, Vitale M, et al.. Crosstalk between decidual NK and CD14+ myelomonocytic cells results in induction of Tregs and immunosuppression. *Proc Natl Acad Sci U S A*. 2010;107:11918–11923. doi:10.1073/pnas.1001749107
86. Munn DH, Zhou M, Attwood JT, et al.. Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science*. 1998;281:1191–1193. doi:10.1126/science.281.5380.1191
87. Zhang J, Dunk C, Croy AB, Lye SJ. To serve and to protect: the role of decidual innate immune cells on human pregnancy. *Cell Tissue Res*. 2016;363:249–265. doi:10.1007/s00441-015-2315-4
88. 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;89:102. doi:10.1095/biolreprod.113.110445
89. Wang S, Qian J, Sun F, et al.. Bidirectional regulation between 1st trimester HTR8/SVneo trophoblast cells and in vitro differentiated Th17/Treg cells suggest a fetal-maternal regulatory loop in human pregnancy. *Am J Reprod Immunol*. 2019;81:e13106. doi:10.1111/aji.13106
90. Fu YY, Ren CE, Qiao PY, Meng YH. Uterine natural killer cells and recurrent spontaneous abortion. *Am J Reprod Immunol*. 2021;86:e13433.
91. Díaz-Hernández I, Alecsandru D, García-Velasco JA, Domínguez F. Uterine natural killer cells: from foe to friend in reproduction. *Hum Reprod Update*. 2021;27:720–746. doi:10.1093/humupd/dmaa062
92. Heikkinen J, Möttönen M, Alanen A, Lassila O. Phenotypic characterization of regulatory T cells in the human decidua. *Clin Exp Immunol*. 2004;136:373–378. doi:10.1111/j.1365-2249.2004.02441.x
93. Dimova T, Nagaeva O, Stenqvist AC, et al.. Maternal Foxp3 expressing CD4+ CD25+ and CD4+ CD25- regulatory T-cell populations are enriched in human early normal pregnancy decidua: a phenotypic study of paired decidual and peripheral blood samples. *Am J Reprod Immunol*. 2011;66(1):44–56. doi:10.1111/j.1600-0897.2011.01046.x
94. Salvany-Celades M, van der Zwan A, Benner M, et al.. Tilburgs T: three types of functional regulatory T Cells Control T cell responses at the human maternal-fetal interface. *Cell Rep*. 2019;27:2537–2547.e5. doi:10.1016/j.celrep.2019.04.109
95. Zare M, Namavar Jahromi B, Gharesi-Fard B. Analysis of the frequencies and functions of CD4(+)CD25(+)CD127(low/neg), CD4(+)HLA-G(+), and CD8(+)HLA-G(+) regulatory T cells in pre-eclampsia. *J Reprod Immunol*. 2019;133:43–51. doi:10.1016/j.jri.2019.06.002
96. Hsu P, Santner-Nanan B, Joung S, Peek MJ, Nanan R. Expansion of CD4(+) HLA-G(+) T Cell in human pregnancy is impaired in pre-eclampsia. *Am J Reprod Immunol*. 2014;71:217–228. doi:10.1111/aji.12195
97. Huang YH, Zozulya AL, Weidenfeller C, Schwab N, Wiendl H. T cell suppression by naturally occurring HLA-G-expressing regulatory CD4+ T cells is IL-10-dependent and reversible. *J Leukoc Biol*. 2009;86:273–281. doi:10.1189/jlb.1008649
98. Levings MK, Bacchetta R, Schulz U, Roncarolo MG. The role of IL-10 and TGF-beta in the differentiation and effector function of T regulatory cells. *Int Arch Allergy Immunol*. 2002;129:263–276. doi:10.1159/000067596
99. Sanjabi S, Oh SA, Li MO. Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. *Cold Spring Harb Perspect Biol*. 2017;9:a022236. doi:10.1101/cshperspect.a022236
100. Zhang J, Dunk CE, Shynlova O, Caniggia I, Lye SJ. TGFb1 suppresses the activation of distinct dNK subpopulations in preeclampsia. *EBioMedicine*. 2019;39:531–539. doi:10.1016/j.ebiom.2018.12.015
101. Häringer B, Lozza L, Steckel B, Geginat J. Identification and characterization of IL-10/IFN-gamma-producing effector-like T cells with regulatory function in human blood. *J Exp Med*. 2009;206:1009–1017.
102. Akdis M, Verhagen J, Taylor A, et al.. Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med*. 2004;199:1567–1575. doi:10.1084/jem.20032058
103. White AM, Wraith DC. Tr1-Like T cells - an enigmatic regulatory T cell lineage. *Front Immunol*. 2016;7:355. doi:10.3389/fimmu.2016.00355
104. Niedzielska M, Israelsson E, Angermann B, et al.. Differential gene expression in human tissue resident regulatory T cells from lung, colon, and blood. *Oncotarget*. 2018;9:36166–36184. doi:10.18632/oncotarget.26322
105. Weiner HL. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. *Immunol Rev*. 2001;182:207–214. doi:10.1034/j.1600-065X.2001.1820117.x
106. Elkord E, Abd Al Samid M, Chaudhary B. Helios, and not FoxP3, is the marker of activated Tregs expressing GARP/LAP. *Oncotarget*. 2015;6:20026–20036.
107. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol*. 2004;5:266–271. doi:10.1038/ni1037
108. Woidacki K, Meyer N, Schumacher A, Goldschmidt A, Maurer M, Zenclussen AC. Transfer of regulatory T cells into abortion-prone mice promotes the expansion of uterine mast cells and normalizes early pregnancy angiogenesis. *Sci Rep*. 2015;5:13938. doi:10.1038/srep13938

109. Keller CC, Eikmans M, van der Hoorn MP, Lashley L. Recurrent miscarriages and the association with regulatory T cells; A systematic review. *J Reprod Immunol*. 2020;139:103105. doi:10.1016/j.jri.2020.103105
110. Banerjee P, Jana SK, Pasricha P, Ghosh S, Chakravarty B, Chaudhury K. Proinflammatory cytokines induced altered expression of cyclooxygenase-2 gene results in unreceptive endometrium in women with idiopathic recurrent spontaneous miscarriage. *Fertil Steril*. 2013;99:179–187.e2. doi:10.1016/j.fertnstert.2012.08.034
111. Yang X, Tian Y, Zheng L, Luu T, Kwak-Kim J. The Update Immune-Regulatory Role of Pro- and Anti-Inflammatory Cytokines in Recurrent Pregnancy Losses. *Int J Mol Sci*. 2022;24:132. doi:10.3390/ijms24010132
112. Kwak-Kim J, Bao S, Lee SK, Kim JW, Gilman-Sachs A. Immunological modes of pregnancy loss: inflammation, immune effectors, and stress. *Am J Reprod Immunol*. 2014;72:129–140. doi:10.1111/aji.12234
113. Lissauer D, Goodyear O, Khanum R, Moss PA, Kilby MD. Profile of maternal CD4 T-cell effector function during normal pregnancy and in women with a history of recurrent miscarriage. *Clin Sci (Lond)*. 2014;126:347–354. doi:10.1042/CS20130247
114. Lédée N, Munaut C, Aubert J, et al.. Specific and extensive endometrial deregulation is present before conception in IVF/ICSI repeated implantation failures (IF) or recurrent miscarriages. *J Pathol*. 2011;225:554–564. doi:10.1002/path.2948
115. Zhao X, Jiang Y, Wang L, Li Z, Li Q, Feng X. Advances in understanding the immune imbalance between T-Lymphocyte Subsets and NK cells in recurrent spontaneous abortion. *Geburtshilfe Frauenheilkd*. 2018;78(7):677–683. doi:10.1055/a-0634-1813
116. Cubro H, Kashyap S, Nath MC, Ackerman AW, Garovic VD. The role of interleukin-10 in the pathophysiology of preeclampsia. *Curr Hypertens Rep*. 2018;20:36. doi:10.1007/s11906-018-0833-7
117. Kedzierska AE, Lorek D, Slawek A, Chelmonska-Soyta A. Tregitopes regulate the tolerogenic immune response and decrease the foetal death rate in abortion-prone mouse matings. *Sci Rep*. 2020;10:10531. doi:10.1038/s41598-020-66957-z
118. Granne I, Shen M, Rodriguez-Caro H, et al.. Characterisation of peri-implantation endometrial Treg and identification of an altered phenotype in recurrent pregnancy loss. *Mucosal Immunol*. 2022;15:120–129. doi:10.1038/s41385-021-00451-1
119. Yang H, Qiu L, Chen G, Ye Z, C L, Lin Q. Proportional change of CD4+CD25+ regulatory T cells in decidua and peripheral blood in unexplained recurrent spontaneous abortion patients. *Fertil Steril*. 2008;89:656–661. doi:10.1016/j.fertnstert.2007.03.037
120. Jin LP, Chen QY, Zhang T, Guo PF, Li DJ. The CD4+CD25 bright regulatory T cells and CTLA-4 expression in peripheral and decidual lymphocytes are down-regulated in human miscarriage. *Clin Immunol*. 2009;133:402–410. doi:10.1016/j.clim.2009.08.009
121. Inada K, Shima T, Nakashima A, Aoki K, Ito M, Saito S. Characterization of regulatory T cells in decidua of miscarriage cases with abnormal or normal fetal chromosomal content. *J Reprod Immunol*. 2013;97:104–111. doi:10.1016/j.jri.2012.12.001
122. Sasaki Y, Sakai M, Miyazaki S, Higuma S, Shiozaki A, Saito S. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *Mol Hum Reprod*. 2004;10:347–353. doi:10.1093/molehr/gah044
123. Wang WJ, Hao CF, Yi-Lin Y, Bao GJ, Qiu SH, Lin LH. QD: increased prevalence of T helper 17 (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. *J Reprod Immunol*. 2010;84:164–170. doi:10.1016/j.jri.2009.12.003
124. Robertson SA, Sharkey DJ. Seminal fluid and fertility in women. *Fertil Steril*. 2016;106:511–519. doi:10.1016/j.fertnstert.2016.07.1101
125. Omenetti S, Pizarro TT. The Treg/Th17 Axis: a dynamic balance regulated by the gut microbiome. *Front Immunol*. 2015;6:639. doi:10.3389/fimmu.2015.00639
126. Sadlon T, Brown CY, Bandara V, et al.. Unravelling the molecular basis for regulatory T-cell plasticity and loss of function in disease. *Clin Transl Immunology*. 2018;7:e1011.
127. Schjenken JE, Zhang B, Chan HY, Sharkey DJ, Fullston T, Robertson SA. mi RNA Regulation of Immune Tolerance in Early Pregnancy. *Am J Reprod Immunol*. 2016;75:272–280. doi:10.1111/aji.12490
128. Hori S. Lineage stability and phenotypic plasticity of Foxp3□ regulatory T cells. *Immunol Rev*. 2014;259:159–172. doi:10.1111/imr.12175
129. Liu C, Wang XZ, Sun XB. Assessment of sperm antigen specific T regulatory cells in women with recurrent miscarriage. *Early Hum Dev*. 2013;89:95–100. doi:10.1016/j.earlhumdev.2012.08.003
130. Bettelli E, Carrier Y, Gao W, et al.. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature*. 2006;441:235–238. doi:10.1038/nature04753
131. Zhao J, Zhao J, Perlman S. Differential effects of IL-12 on Tregs and non-Treg T cells: roles of IFN-γ, IL-2 and IL-2R. *PLoS One*. 2012;7:e46241.
132. Prins JR, Zhang B, Schjenken JE, Guerin LR, Barry SC, Robertson SA. Unstable Foxp3+ regulatory T cells and altered dendritic cells are associated with lipopolysaccharide-induced fetal loss in pregnant interleukin 10-deficient mice. *Biol Reprod*. 2015;93:95. doi:10.1095/biolreprod.115.128694
133. Rowe JH, Ertelt JM, Aguilera MN, Farrar MA, Way SS. Foxp3(+) regulatory T cell expansion required for sustaining pregnancy compromises host defense against prenatal bacterial pathogens. *Cell Host Microbe*. 2011;10:54–64. doi:10.1016/j.chom.2011.06.005
134. Robertson SA. Immune regulation of conception and embryo implantation-all about quality control. *J Reprod Immunol*. 2010;85:51–57. doi:10.1016/j.jri.2010.01.008
135. Mazziotta C, Pellielo G, Tognon M, Martini F, Rotondo JC. Significantly low levels of igg antibodies against oncogenic Merkel cell polyomavirus in sera from females affected by spontaneous abortion. *Front Microbiol*. 2021;12:789991. doi:10.3389/fmicb.2021.789991
136. D'Addio F, Riella LV, Mfarrej BG, et al.. The link between the PDL1 costimulatory pathway and Th17 in fetomaternal tolerance. *J Immunol*. 2011;187:4530–4541. doi:10.4049/jimmunol.1002031
137. Chang J-H, Xiao Y, Hu H, et al.. Ubc13 maintains the suppressive function of regulatory T cells and prevents their conversion into effector-like T cells. *Nat Immunol*. 2012;13(5):481–490. doi:10.1038/ni.2267
138. Steinborn A, Schmitt E, Kisielewicz A, et al.. Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T cell (Treg) pool with distinct subsets of Tregs. *Clin Exp Immunol*. 2012;167:84–98. doi:10.1111/j.1365-2249.2011.04493.x
139. Bluestone JA, Trotta E, Xu D. The therapeutic potential of regulatory T cells for the treatment of autoimmune disease. *Expert Opin Ther Targets*. 2015;19:1091–1103. doi:10.1517/14728222.2015.1037282
140. Zhang Q, Wang HY, Marzec M, Raghunath PN, Nagasawa T, Wasik MA. STAT3- and DNA methyltransferase 1-mediated epigenetic silencing of SHP-1 tyrosine phosphatase tumor suppressor gene in malignant T lymphocytes. *Proc Natl Acad Sci U S A*. 2005;102:6948–6953. doi:10.1073/pnas.0501959102

141. Hodge DR, Cho E, Copeland TD, et al.. IL-6 enhances the nuclear translocation of DNA cytosine-5-methyltransferase 1 (DNMT1) via phosphorylation of the nuclear localization sequence by the AKT kinase. *Cancer Genomics Proteomics*. 2007;4:387–398.
142. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol*. 2010;40:1830–1835. doi:10.1002/eji.201040391
143. Raffin C, Vo LT, Bluestone JA. T(reg) cell-based therapies: challenges and perspectives. *Nat Rev Immunol*. 2020;20:158–172. doi:10.1038/s41577-019-0232-6
144. Nishimoto N, Yoshizaki K, Miyasaka N, et al.. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2004;50:1761–1769. doi:10.1002/art.20303
145. Ito H, Takazoe M, Fukuda Y, et al.. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology*. 2004;126:989–996. doi:10.1053/j.gastro.2004.01.012
146. Illei GG, Shirota Y, Yarboro CH, et al.. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. *Arthritis Rheum*. 2010;62:542–552. doi:10.1002/art.27221
147. Abbas AK, Trotta E, Simeonov D, Marson A, Bluestone JA. Revisiting IL-2: biology and therapeutic prospects. *Sci Immunol*. 2018;3:eaat1482. doi:10.1126/sciimmunol.aat1482
148. Barron L, Dooms H, Hoyer KK, et al.. Cutting edge: mechanisms of IL-2-dependent maintenance of functional regulatory T cells. *J Immunol*. 2010;185:6426–6430. doi:10.4049/jimmunol.0903940
149. Boardman DA, Levings MK. Cancer immunotherapies repurposed for use in autoimmunity. *Nat Biomed Eng*. 2019;3:259–263. doi:10.1038/s41551-019-0359-6
150. Tang Q, Adams JY, Penaranda C, et al.. Central role of defective interleukin-2 production in the triggering of islet autoimmune destruction. *Immunity*. 2008;28:687–697. doi:10.1016/j.immuni.2008.03.016
151. Grinberg-Bleyer Y, Baeyens A, You S, et al.. IL-2 reverses established type 1 diabetes in NOD mice by a local effect on pancreatic regulatory T cells. *J Exp Med*. 2010;207:1871–1878. doi:10.1084/jem.20100209
152. Trotta E, Bessette PH, Silveria SL, et al.. A human anti-IL-2 antibody that potentiates regulatory T cells by a structure-based mechanism. *Nat Med*. 2018;24:1005–1014. doi:10.1038/s41591-018-0070-2
153. Ito S, Bollard CM, Carlsten M, et al.. Ultra-low dose interleukin-2 promotes immune-modulating function of regulatory T cells and natural killer cells in healthy volunteers. *Mol Ther*. 2014;22:1388–1395. doi:10.1038/mt.2014.50
154. Winger EE, Reed JL. Low circulating CD4(+) CD25(+) Foxp3(+) T regulatory cell levels predict miscarriage risk in newly pregnant women with a history of failure. *Am J Reprod Immunol*. 2011;66:320–328. doi:10.1111/j.1600-0897.2011.00992.x
155. Mohammadi S, Abdollahi E, Nezamnia M, et al. Adoptive transfer of Tregs: a novel strategy for cell-based immunotherapy in spontaneous abortion: lessons from experimental models. *Int Immunopharmacol*. 2021;90:107195. doi:10.1016/j.intimp.2020.107195
156. Siddiqui I, Erreni M, van Brakel M, Debets R, Allavena P. Enhanced recruitment of genetically modified CX3CR1-positive human T cells into Fractalkine/CX3CL1 expressing tumors: importance of the chemokine gradient. *J Immunother Cancer*. 2016;4:21. doi:10.1186/s40425-016-0125-1
157. Garetto S, Sardi C, Martini E, et al.. Tailored chemokine receptor modification improves homing of adoptive therapy T cells in a spontaneous tumor model. *Oncotarget*. 2016;7:43010–43026. doi:10.18632/oncotarget.9280
158. Idorn M, Skadborg SK, Kellermann L, et al.. Chemokine receptor engineering of T cells with CXCR2 improves homing towards subcutaneous human melanomas in xenograft mouse model. *Oncoimmunology*. 2018;7:e1450715.
159. Zhang L, Long X, Yin Y, et al.. Histone methyltransferase Nsd2 ensures maternal-fetal immune tolerance by promoting regulatory T-cell recruitment. *Cell Mol Immunol*. 2022;19:634–643. doi:10.1038/s41423-022-00849-2
160. Motwani K, Peters LD, Vliegen WH, et al.. Human regulatory T cells from umbilical cord blood display increased repertoire diversity and lineage stability relative to adult peripheral blood. *Front Immunol*. 2020;11:611. doi:10.3389/fimmu.2020.00611
161. Jagger A, Shimojima Y, Goronzy JJ, Weyand CM. Regulatory T cells and the immune aging process: a mini-review. *Gerontology*. 2014;60:130–137. doi:10.1159/000355303
162. Carbone F, La Rocca C, De Candia P, et al.. Metabolic control of immune tolerance in health and autoimmunity. *Semin Immunol*. 2016;28:491–504. doi:10.1016/j.smim.2016.09.006
163. Murai M, Krause P, Cheroutre H, Kronenberg M. Regulatory T-cell stability and plasticity in mucosal and systemic immune systems. *Mucosal Immunol*. 2010;3:443–449. doi:10.1038/mi.2010.27
164. Amersfoort J, Kuiper J. T cell metabolism in metabolic disease-associated autoimmunity. *Immunobiology*. 2017;222:925–936. doi:10.1016/j.imbio.2017.03.001
165. Issazadeh-Navikas S, Teimer R, Bockermann R. Influence of dietary components on regulatory T cells. *Mol Med*. 2012;18:95–110. doi:10.2119/molmed.2011.00311
166. Sharkey DJ, Tremellen KP, Briggs NE, Dekker GA, Robertson SA. Seminal plasma pro-inflammatory cytokines interferon-γ (IFNG) and C-X-C motif chemokine ligand 8 (CXCL8) fluctuate over time within men. *Hum Reprod*. 2017;32:1373–1381. doi:10.1093/humrep/dex106
167. Robertson SA, Moldenhauer LM, Green ES, Care AS, Hull ML. Immune determinants of endometrial receptivity: a biological perspective. *Fertil Steril*. 2022;117:1107–1120. doi:10.1016/j.fertnstert.2022.04.023
168. Yamazaki S, Nishioka A, Kasuya S, et al.. Homeostasis of thymus-derived Foxp3+ regulatory T cells is controlled by ultraviolet B exposure in the skin. *J Immunol*. 2014;193:5488–5497. doi:10.4049/jimmunol.1400985
169. Burzyn D, Kuswanto W, Kolodin D, et al.. A special population of regulatory T cells potentiates muscle repair. *Cell*. 2013;155:1282–1295. doi:10.1016/j.cell.2013.10.054
170. Li J, Chen Y, Liu C, Hu Y, Li L. Intravenous immunoglobulin treatment for repeated IVF/ICSI failure and unexplained infertility: a systematic review and a meta-analysis. *Am J Reprod Immunol*. 2013;70:434–447. doi:10.1111/aji.12170
171. Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. *Am J Reprod Immunol*. 2008;60:8–16. doi:10.1111/j.1600-0897.2008.00585.x
172. Tempfer CB, Kurz C, Bentz EK, et al.. A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study. *Fertil Steril*. 2006;86:145–148. doi:10.1016/j.fertnstert.2005.12.035
173. Vomstein K, Feil K, Strobel L, et al.. Immunological risk factors in recurrent pregnancy loss: guidelines versus current state of the art. *J Clin Med*. 2021;10:869. doi:10.3390/jcm10040869

174. 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;187:1778–1787. doi:10.4049/jimmunol.1003919
175. Lee JH, Lydon JP, Kim CH. Progesterone suppresses the mTOR pathway and promotes generation of induced regulatory T cells with increased stability. *Eur J Immunol*. 2012;42:2683–2696. doi:10.1002/eji.201142317
176. Piccinni MP, Scaletti C, Maggi E, Romagnani S. Role of hormone-controlled Th1- and Th2-type cytokines in successful pregnancy. *J Neuroimmunol*. 2000;109:30–33. doi:10.1016/S0165-5728(00)00299-X