Thieme

Advances in Understanding the Immune Imbalance between T-Lymphocyte Subsets and NK Cells in Recurrent Spontaneous Abortion

Fortschritte im Verständnis des immunologischen Ungleichgewichts zwischen Untergruppen von T-Lymphozyten und natürlichen Killerzellen bei wiederholten Aborten

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ABSTRACT

Recurrent spontaneous abortion is a global problem, and unexplained recurrent abortion triggered by immunological factors is an important focus of current research. Helper T lymphocytes (Th cells) and regulatory T lymphocytes (Treg cells) are central in human immune regulation and play a complex role in pregnancy. Natural killer cells (NK cells) exist in the endometrium and cooperate with T lymphocytes to create immune tolerance at the maternal-fetal interface, which is essential for successful pregnancy. This review has analyzed studies on Th17 cell, Treg cell and NK cell dysfunction and cellular imbalances which may contribute to unexplained recurrent spontaneous abortion to suggest a possible direction for future immunotherapies.

ZUSAMMENFASSUNG

Der habituelle Abort ist ein weltweit auftretendes Problem, und habituelle, durch immunologische Faktoren ausgelöste Aborte unklarer Genese stehen im Mittelpunkt aktueller Forschungen. T-Helfer-Lymphozyten (TH-Zellen) und regulatorische T-Lymphozyten (T-reg-Zellen) sind zentral für die menschliche Immunregulation und spielen eine komplexe Rolle in der Schwangerschaft. In der Uterusschleimhaut gibt es natürliche Killerzellen (NK-Zellen), die mit den T-Lymphozyten zusammenarbeiten, um jene maternofetale Immuntoleranz herzustellen, die für eine erfolgreiche Schwangerschaft unabdingbar ist. In diesem Übersichtsartikel werden Studien zu Funktionsstörungen von TH17-Zellen, T-reg-Zellen und NK-Zellen sowie zum Ungleichgewicht von Zellen vorgestellt. Die besprochenen Funktionsstörungen tragen möglicherweise zum Auftreten von habituellen Aborten bei und deuten auch die potenzielle Forschungsrichtung für künftige Immuntherapien an.

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Introduction

Recurrent spontaneous abortion (RSA) is defined as 3 or more clinically detectable pregnancy losses occurring in the first 20 weeks of pregnancy [1]. RSA is a common complication of pregnancy and accounts for 5% of abortions occurring in women of childbearing age [2]. Although RSAs may have a clear etiology such as uterine anatomical defects, chromosome aberrations, hormone disorders, blood system diseases [3], around 60% of the triggers of RSA remain unexplored [4], the majority of them assumed to be associated with immunological abnormalities. These spontaneous abortions are defined as unexplained recurrent spontaneous abortion (URSA). Pregnancy success is dependent on semi-allogeneic processes. In the maternal body, many different immune cells and factors work together to create an immune tolerance which allows the embryo to successfully evade the maternal immune system. Abnormal immunological mechanisms can result in recurrent pregnancy loss. The immune factors behind recurrent spontaneous abortion are complicated. In addition to autoimmune diseases, the abnormal expression of human leukocyte antigens, Th1/Th2 imbalance [5], Fas ligand expression in embryonic trophoblast cells [6], and the inhibition of complement activation [7], abnormal immune functions of Th17 cells, Treg cells and decidual natural killer (dNK) cells and imbalances in these three types of cells also play a key role in URSA.

Pregnancy and Immunization

The embryo is considered semi-allogeneic because of its expression of the paternal MHC class I antigen (HLA-C) [8]. The paternal antigen expressed in embryonic trophoblast cells, along with its own MHC class II antigen, is delivered to specific CD4+ T helper cells after processing by maternal cells. Under the stimulation of antigens, the original CD4+ T cells differentiate into various T cells, including Th1, Th2, Th17 [9] and regulatory T (Treg) cells [10]. CD4+ Th1 cells produce interleukin (IL-2), tumor necrosis factor (TNF-α) and interferon (IFN-γ), the main effectors of phagocytes that mediate host defense and are highly lethal to intracellular infection. CD4+ Th2 cells are mainly responsible for the phagocytosis of extracellular parasites, including nematodes, and produce IL-5 and IL-4 that can promote the growth and differentiation of eosinophil. IL-4 accompanied by IL-13 can also inhibit the function of macrophages by stimulating IgE and IgG1 antibodies [11]. In a normal pregnancy, Th1 and Th2 cell responses show a physiological imbalance, with Th2-type cells prevailing at the maternal-fetal interface and thus playing a role in the immune protection of embryo. However, overexpression of Th1-type cytokines was found in URSA [12], and immune damage is the result of an overactive immune response, leading to loss of the embryo. Th17 cells secrete many pro-inflammatory factors which are responsible for autoimmune diseases, inflammatory states and non-self discrimination (immune rejection). In pregnancy, fetal cells may be rejected due to an increase in Th17 cells. Treg cells can hinder the effect of T cells to maintain immune tolerance at the maternal-fetal interface. Natural killer cells (NK) are important components of the human immune system. Unlike peripheral blood NK cells, the specific surface molecules of dNK cells secrete cytokines that regulate trophoblast invasion and participate in the remodeling of the uterine spiral arteries during pregnancy, which is particularly important in early pregnancy. In short, the coordination of various types of cells and factors contributes to the formation of an immune-tolerant micro-environment.

Th17 cells

Th17 cells are subsets of CD4+ T cells which secrete the pro-inflammatory cytokine interleukin-17 (IL-17) [13]. Retinoic acid orphan nuclear receptor (RORC) is a key regulatory transcription factor in the differentiation of human Th17 cells [14]. Unlike mice, the production of Th17 cells in humans does not require transforming growth factor-β (TGF-β) and IL-6. IL-1 β and IL-23 are the most effective cytokines that initiate Th17 cell differentiation [15]. After differentiation, Th17 cells secrete IL-21 which increases differentiation and activates the STAT3 signaling pathway even further to induce the expression of retinoic acid-related nuclear receptor-γt (RORγt). IL-23 is responsible for maintaining the stability and maturity of Th17 cells in the later stages of differentiation [16]. In contrast, IFN-γ, IL-4 and IL-27 inhibit the formation of Th17 cells [17]. Th17 cells are a major subgroup of CD4+ T cells and play a vital role in inducing inflammation due to the functions of IL-17, IL-22 and TNF-α. Th17 cells promote the formation of pro-inflammatory cytokines such as IL-17A, IL-17F, IL-22, IL-6, TNF-α and matrix metalloproteinases [18] and activate epithelial cells, macrophages, fibroblasts and endothelial cells to combat extracellular bacterial infection and tumors, thereby playing an essential role in inflammatory processes and the immune rejection of organ transplants [19].

Th17 cells and pregnancy

Fetal alloantigens can stimulate Th17 cells to secrete a variety of pro-inflammatory cytokines to induce fetal rejection [20]. Huber et al. [21] have reported on the accumulation of IL-17-positive T cells in the decidual tissue of women with RSA. Wang et al. [22] found that levels of Th17 CCR6+ cells, cytokines IL-17 and IL-23 and RORC mRNA were significantly higher in the decidua and peripheral blood of women with RSA than in women with normal pregnancies. Compared with the control group, IL-27, a key regulator of Th17 cells, was significantly reduced in the decidua of patients with URSA [23]. Scientists are continuing to explore the immune mechanisms of Th17 cells that lead to recurrent miscarriage. Nakashima et al. [24] suggested that Th17 cells may contribute to abortions through inflammatory responses in late pregnancy rather than in the early stages of pregnancy. Soheil et al. [25] explored the relationship between Th17 and URSA at the genetic level and suggested that an IL-17F gene polymorphism may be associated with recurrent pregnancy loss. A case-control study which investigated 85 healthy women who had successfully given birth at least once and compared them to women with RSA was carried out. PCR was used to analyze the frequency of IL-17F, IL-17A and IL-17R polymorphisms. The researchers found that the genotype frequency of IL-17Frs763780 was significantly decreased in the group of women with RSA compared to the control group. The cytokines produced by IL-17Frs763780 genotypes

cannot induce pro-inflammatory cytokines and chemokines, which could reduce the possibility of miscarriage. Are Th17 cells bad for pregnancy? The issue is still controversially discussed. Nakashima et al. [26] investigated the levels of Th17 cells in peripheral blood in the first, second and third trimesters of pregnancy, and found that numbers of Th17 cells were constant during pregnancy, indicating that Th17 cells could effectively tolerate pregnancy. Some studies have even suggested that Th17 cells may be beneficial for pregnancy. A recent study showed that IL-17 can increase progesterone secretion in human chorionic trophoblast cell lines [27]. Elevated progesterone levels can promote progesterone-induced blocking factor (PIBF) production, which increases protection during pregnancy [28].

Treg cells

Several types of Treg cells have been identified, including CD8+ Treg cells, regulatory T cells producing interleukin-10 (TR1), regulatory T cells producing TGF-β (Th3), and CD4+ CD25+ regulatory T cells [29]. CD4+ CD25+ FOXP3+ Treg cells are one of the most important subgroups of immunomodulatory cells. Two forms of these cells have been identified: naturally regulated T cells differentiated in the thymus, and induced Treg cells which were induced by the specific stimulation of the peripheral antigen. The suppression of immune activity by Treg cells depends on at least two pathways:

1. The expression of co-suppressor molecules through intercellular contact, such as programmed death factor-1 (PD-1) and cytotoxic T lymphocyte antigen CTLA-4 [30];
2. The secretion of immunosuppressive cytokines, such as transforming growth factor β (TGF-β) and IL-10 [31].

Treg cells and pregnancy

The importance of Treg cells in pregnancy has been widely confirmed, and a decrease in the number of Treg cells is associated with an increase in the rate of embryo loss [32]. Based on studies on the depletion and transfer of Treg cells in pregnant mice, it was confirmed that Treg cells play a key role in successful embryo implantation and pregnancy. It has been reported that a depletion of Treg cells prior to embryo implantation can lead to more comprehensive effector T-cell infiltration, giving rise to inflammation in the uterine micro-environment and resulting in implantation failure [33]. Other studies have looked at the relationship between the numbers of Treg cells at different stages in pregnancy and pregnancy outcomes, excluding the period of implantation. Mjösberg et al. [34] observed changes in the numbers of Treg cells during normal pregnancies. He found CD4+ CD25bright Treg cells and CD4+ CD25+ Treg cells increased in early pregnancy, peaked mid-pregnancy, and decreased to low levels in late pregnancy and parturition. Experimental results have suggested that Treg cells might not be necessary to maintain a pregnancy to term. Moreover, the reduction of Treg cells at the end of pregnancy may create favorable conditions for the initiation of childbirth. In animal experiments, Shima et al. [35] showed that a depletion of Treg cells after embryo implantation did not affect pregnancy outcomes in mice, confirming Mjösberg's conjecture. Arruvito et al. [36] studied changes in the number of Treg cells in healthy women and women with URSA at different stages of the menstrual cycle to explore the relationship between Treg cells and URSA. They found that the levels of CD4+ FOXP3+ Treg cells in the peripheral blood of URSA women were significantly lower compared with non-pregnant healthy women in the proliferative or follicular phase of the menstrual cycle. However, the number of Treg cells did not change significantly in the secretory or luteal phase. It was speculated that a decrease of Treg cells in the proliferative phase could be an important cause of recurrent embryo loss [37]. It was suggested that in normal healthy women, increased numbers of Treg cells in the late follicular phase could effectively reduce endometrial inflammation and induce a good immune-tolerant micro-environment. A significant decrease in the number of Treg cells in the secretory phase contributed to the uncomplicated completion of the inflammatory process of implantation.

However, Treg cells do not always have a beneficial effect on pregnancy. Some studies have reported that the adoptive transfer of Treg cells from pregnant mice into abortion-prone mice could prevent embryo loss [38]. However, the rate of embryo loss could not be reduced by implanting Treg cells from healthy non-pregnant mice into mice prone to abortion. It was shown that Treg cells could invade the maternal-fetal interface, but Treg cells only had protective regulatory effect after identification of the paternal antigen. Moreover, Treg cells introduced in a polyinosinic-polycytidylic acid [poly(I:C)] micro-environment not only had no positive effect on pregnancy but also induced NF-κB transcription to produce harmful effects on pregnancy outcomes [39].

NK cells

NK cells are large granular lymphocytes of the innate immune system. Mature pNK cells in blood account for ~ 5–20% of total lymphocytes. They are the first line of defense when a host is invaded by a pathogen [40]. Unlike the immune mechanism of T cells (which express antigen-specific receptors), NK cell activity is regulated by the dynamic signal balance between inhibitory and activating receptors on the surface of NK cells interacting with specific ligands on target cells [41]. Studies have shown that NK cells are not only cytotoxic to tumor cells or infected cells, but also secrete various cytokines which regulate the functions of other immune cells [42]. Raulet et al. [43] showed that NK cells could regulate the adaptive immune response through interaction with dendritic cells, T cells and cytokines as well as through cell-to-cell contact, thus bridging innate and adaptive immunity.

NK cells and pregnancy

The phenotypic characteristics of dNK in normal pregnant women are CD56bright CD16, while the phenotypic characteristics of pNK cells are CD56dimCD16+ [44]. pNK cells can express intact activation receptors including NKp46, NKp30 and NKG2D [45], while dNK cells only express NKp44 receptors [46], which cannot make uNK cells form active immune synapses with target cells. Some studies have reported that a decrease in the expression of NKp44 receptors is associated with reproductive failure [47]. This shows that dNK cells which lose the killer phenotype provide a micro-environment compatible with the embryo which supports a healthy pregnancy [48]. In the pre-ovulation phase of the menstrual cycle,

only a few granular dNK cells exist in the endometrium. In the secretory phase, the number of dNK cells increases sharply as the progesterone levels increase. If a pregnancy ensues, the number of dNK cells increases even further, accounting for 60–90% of decidual immune cells [49] and becoming the main immune cells at the interface during early human pregnancy and then decreasing in mid- and late pregnancy. dNK cells are therefore considered to play a key immunomodulatory role in early pregnancy. However, the exact immune function of these NK cells is not yet clear and is still being investigated. Some researchers believe that dNK cells do not participate in the implantation of the embryo but contribute by participating in the changes to the vascular and spiral artery structure of the endometrium [50]. In early pregnancy, human uNK cells can secrete a variety of potent angiogenic factors, including VEGF-C, IL-8, IP-10, placental growth factor antibody and angiopoietin [51] to produce a low-resistance uterine circulation which promotes trophoblast invasion and the transmission of blood, nutrition and oxygen between the maternal placenta and the fetus. Soares [52] and colleagues showed that depletion of NK cells in rats induced hypoxia and delayed the initiation of spiral artery remodeling, while a recovery in the number of dNK cells corrected these deficiencies. Kroy et al. [53] also reported that IFN-γ secreted by dNK cells supports remodeling of the arteries. At the same time, dNK cells are also involved in the creation of immune tolerance [54]. During in vivo experiments, it was observed that continuous exposure of dNK cell receptors to the ligands of invasive trophoblast cells stimulated the activation receptors of the dNK cells in a chronic manner, resulting in the NK cells' tolerance to embryonic cells and enhancing their ability to secrete growth factors [55]. These two key physiological functions of dNK cells are necessary for placental growth and a normal pregnancy. However, dNK cells are not always beneficial to pregnancy. Co et al. [56] showed that NK cells might return to the killing phenotype under the conditions of in vitro culture or without IL-2 stimulation, which indicates that the micro-environment of the decidua supports the development of its immune tolerance phenotype.

The Equilibrium Relationship between Cells

Th17 and Treg cells

Th17/Treg cells are actively involved in establishing immune tolerance and immune defense. A healthy immune system not only recognizes and resists infection, it also regulates the immune response to self-tissue antigens and harmless non-self-organisms. In pregnancy, fetal antigens challenge the maternal immune system, while Treg cells are responsible for regulating Th17 cells and protecting the embryo against maternal rejection which protects the mother from infection [57]. Maternal-fetal immune tolerance is regulated by the balance between these two types of cells. When the level of Th17 cells increases and the level of Treg cell decreases, the incidence of RSA was found to increase [58]. Nasrin et al. [59] used flow cytometry to detect the ratio of Th17/Treg cells in the peripheral blood of URSA women and normal non-pregnant women. The ratio of Th17/Treg cells in the URSA group increased during the proliferative stage of the menstrual cycle, and no changes occurred in the secretory stage. These findings seem to show that an imbalance in the ratio of Th17/Treg cells in the proliferative stage may be a cause of recurrent abortion.

It has been reported that Th17 cells and Treg cells can take on each other's characteristics, and that this plasticity is affected by the cytokine environment [60]. Recent studies have shown that there are cells which express IL-17/FOXP3 [61] and interferon γ/IL17 [62] at the same time, and that these cells may be transient phenotypes occurring during cell conversion. Some researchers are of the opinion that the IL-6 secreted by dendritic cells is the key factor which regulates the transformation of Treg cells and Th17 cells. An experiment showed that when only TGF-β was present, the initial CD4+T cells were induced to differentiate into Treg cells, but when TGF-β and IL-6 were present together, they differentiated into Th17 cells [63]. It has been shown that the phenotypes of Treg cells and Th17 cells are not stable. In patients with RSA affected by an infection or endocrine factors, the mechanism regulating the balance between the two cell types can become damaged, resulting in a vicious cycle of repeated embryo loss.

Treg cells and dNK cells

The synergy between Treg cells and dNK cells is essential to maintain the immune micro-environment required for normal pregnancy. NK cells have been shown to promote the amplification of regulatory T cells [64]. Sasaki et al. [65] found that increases in NK cells increased CD4+ CD25bright Treg cells and that the expression of cytotoxic T lymphocyte antigen 4 (CTLA-4) was higher at the interface in women in the early stage of pregnancy compared to a group of non-pregnant women. Vacca et al. [66] suggested that dNK cells stimulated the proliferation and secretion of Treg cells by interacting with CD14+. This suggestion was confirmed by Hsu et al. [67], who found that the induction of immune-tolerance models during pregnancy required a high expression of tolerance molecules by CD14+DC-SIGN+APC cells (CD14+ dendritic cell-specific intercellular adhesion molecule-3 combined with non-integrin factors + antigen-presenting cells), such as immunoglobulin-like transcript 4 (ILT4) receptor and human leukocyte antigen-G (HLA-G), which promote the transformation of CD4+ T cells into Treg cells and inhibit the expression of traditional T cells. The changes to the immune mechanism require the stimulation of IL-10. In conclusion, these results emphasize that dNK cells, Treg cells and soluble factor IL-10 work together to create a positive feedback cycle conducive to immune tolerance [68].

dNK cells and Th17 cells

It has been confirmed in human trials that dNK cells produce immune tolerance towards the embryo at the maternal-fetal interface by inhibiting the formation of Th17 cells. Huber et al. [69] obtained decidual tissue from RSA patients and studied the ratio of CD27+ NK/TH17 cells. They found that the ratio was significantly decreased in women with RSA, and that IL-10, a key factor responsible for inhibiting Th17 cells, was also significantly lower, suggesting that the regulatory function of NK cells in patients with RSA was impaired and was accompanied by an increased Th17 cell response and extensive local inflammation. To explore the regula-

tory effect of NK cells on Th17 cells in vivo, Fu et al. [70] developed animal experiments to deplete NK cells in mice, extracted decidual tissue and isolated Th17 cells. Their results showed that the percentage of Th17 cells in the NK cell-depleted group was 11.97 + 0.9273 %, which was significantly higher than in the control group (6.497 + 0.5792 %), which further confirmed the regulatory effect of NK cells on Th17 cells. Some studies [72] have suggested that dNK cells inhibit Th17 cells by reducing the IFN-γ produced by the subset of CD56brightCD27+ dNK cells. Studies have shown that when IFN-γ secreted by dNK cells was neutralized, dNK cells no longer controlled Th17 cell polarization, leading to decidual inflammation with loss of immune tolerance at the maternal-fetal interface and abnormal pregnancies [71]. It is obvious that the balance between dNK cells and Th17 cells is of great importance for a successful pregnancy.

Summary

Any successful pregnancy is the result of the complex coordination of multiple factors. The cooperation between immune cells and cytokines to mediate or restrain inflammation creates an immune network based on multiple equilibria at the maternal-fetal interface. The immunological abnormalities in URSA are complex and varied, making this an important problem in reproductive medicine. A dysfunction of Th17, Treg and uNK cells in the mother or at the fetal-maternal interface or an immunomodulatory imbalance at the cellular level may play a key role in the occurrence of URSA. A number of studies are currently investigating the issue, but the specific signaling pathways and cytokines which lead to an imbalance of immune regulation are still unclear, and further research is required to provide effective immunotherapy, correct immune imbalances at the maternal-fetal interface, restore the immunological micro-environment required for successful pregnancy, and bring hope to women suffering from recurrent spontaneous abortion.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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