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Approach to immunological abortion & chronic inflammation

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Introduction

Recurrent Spontaneous Abortion (RSA) is a serious reproductive disorder of pregnancy that presents an unresolved issue in the fields of gynecology and obstetrics. RSA is usually defined as a woman suffering from ≥3 spontaneous abortions with the same sexual partner. The incidence rate of RSA ranges from 1 to 5% in women of childbearing age [1]. Recent research has determined that the etiology of RSA is extremely varied, chiefly advanced high maternal age, inheritable genetic abnormalities, anatomical factors, infections, and endocrine dysfunctions. However, in most patients, the cause is unclear. Immune dysfunction accounts for more than half of these cases, and is usually referred to as immune-related RSA. A successful pregnancy requires an accurate immunologic dialogue at the maternal-fetal immune interface in the endometrium [2]. During early gestation, the occurrence of immunologic events over bilateral communication between the mother and fetus is extremely elaborate, and encompasses a great deal of immunocytes, including innate lymphocytes (ILC), macrophages, decidual dendritic cells (DCs), and T cells. These cells play a crucial role in establishing a balance between the inflammatory response and immune tolerance [3]. Existing evidence indicates that disorders occurring in the endometrial immune microenvironment are related to severe crucial reproductive disorders, which involve Recurrent Implantation Failure (RIF) and RSA with inexplicable etiology. Innate Lymphoid Cells Innate lymphoid cells (ILCs) play significant roles in membrane immunity, tissue equilibrium, and metabolism regulation, and have inspired much research in recent years [4,5].

Immunology in pregnancy loss

Researchers have identified that ILCs exist in the human decidua and are crucial at the maternal-fetal interface. ILCs with short antigen receptors substantiate a classical lymphoid cell morphology, depending on two important components (cytokine receptor γ-chain and the transcriptional repressor inhibitor of DNA binding [2]. Based on distinct developmental pathways, they are classified into two subfields: natural killer (NK) cells and non-cytotoxic helper ILCs, including ILC1s, ILC2s, and ILC3s. Decidual natural killer (dNK) cells are the only subset of ILCs with cytotoxicity [6]. Maladjustment of cytotoxic regulation transforms dNK cells into harmful cells and leads to reproductive disorders, including RSA. Its internal mechanisms have

been extensively researched, including the unbalanced expression of activating and inhibiting receptors on the surface of dNK cells This includes the increased presentation of NKG2D and the lack of KIR, the combination of which causes adverse pregnancy outcomes. Furthermore, it has been found that in the mouse uterus, dNK cell cytotoxicity is usually altered by the unbalanced expression between Tumor Necrosis Factor-Like Weak Inducer of Apoptosis TWEAK and its receptors, which could result in abortion [7].

Unexplained pregnancy loss

More than half of the women who experience RSA are diagnosed with unexplained recurrent pregnancy loss. Some of them may suffer immune defects, such as disorganized NK cells or abnormal NK cell subpopulations. The quantity and viability of peripheral blood NK (pNK) cells may also play an important role in RSA development. Women who suffer from RSA generally have higher active performance in the quantity and viability of Pnk cells compared with normal pregnant women [8]. This may be related to the high cytotoxic activity of pNK. Human NK cells are categorized into four types, including NK1, NK2, NK3, and NKrl subsets, based on cytokine production. Among them, NK1 produces IFN-γ and TNF-α, and NK2 excretes IL-4, IL-5, and IL-13 NK3 cells produce TGF-β; and NKr1 cells produce IL-10. In order to achieve a good pregnancy outcome, NK cells may change from type 1 to type 2 immune responses [9]. A previous study presented an obvious type 1 shift in pNK cells in patients with Recurrent Implantation Failure (RIF) or RSA. This suggests that the growth in the NK1/NK2 ratio may be an indicator for the probability of pregnancy failure [10].

In addition, CD56bright/CD16 accounts for almost 90% of uterine NK (uNK) cells . Cells with low cytotoxic activity produce more cytokines. Women with RSA had a smaller number of uNK than fertile controls, indicating that recurrent spontaneous abortion is closely associated with an abnormal proportion of uNK cells [11]. It is well known that uNK cells are indispensable for controlling trophoblast invasion and proliferation Successful pregnancy depends on correct spiral arter remodeling. During the process of placentation, the purpose of invasive Extravillous Trophoblasts (EVTs) moving to the uterus is to remodel vessels. Spiral artery remodeling by EVTs plays an important role in adapting blood flow and delivering nutrients to developing fetuses. Impaired spiral artery remodeling has been linked to early miscarriage. uNK cells are the major source of various cytokines, including GM-CSF, CSF-1, TNF-α, IFN-γ, TGF-β [23], and angiogenic growth factors [12].

A previous study has shown that in women with RSA, the expression profile of angiogenic factors in CD56bright uNK cells displays a significant overexpression of angiogenin, bFGF, and VEGF-A. This may be relevant to the overactive oxygenation and oxidative stress in the mother and fetal immune interface of patients with RSA. Overexpressed angiogenic growth factors cause aberrant endometrial angiogenesis and vascular disorder, including precocious development of endometrial blood vessels and lowered resistance of uterine artery to blood flow and microvessel density, which above have been found to accumulate in women with RSA [13]. A recent study has shown that obesity is associated with adverse reproductive outcomes. This is because a high-fat diet, which is related to impaired vascular remodeling within the uterus,promotes uNK cell activation during pregnancy and altered uNK gene expression [1,14].

Autophagy in pregnancy loss

In recent years, research on autophagy has become popular in the immunological field. Autophagy, a firmly controlled catabolic approach of cellular self-degradation, is defined as a non-apoptotic form with relevance in overstimulated programmed cell death resulting from the stimuli-initiation, and it is substantially a cellular tension reaction and quality regulation mechanism [15]. Autophagy has an important effect on embryonic growth during the early stage of pregnancy. This development is usually associated with reproductive disorders, including abortion and preeclampsi a [13]. A recent study reported that the level of autophagy in the villi of RSA sufferers was remarkably lower than that of selective termination in pregnant women, and suggested that the suppression of trophoblast autophagy causes RSA via IGF-2 secretion and PEG10 reduction [16]. This study demonstrated that a high level of IGF-2 leads to NK cell transformation into a special category of cell with high cytotoxic activity, which then attacks normal cells at the immune interface [17]. The latter has a negative influence on the process of vascular invasion, which induces pregnancy failure. Uterine Dendritic Cells. In the decidua, uterine DCs are believed to play a key role in the delicate equilibrium involved in maternal recognition of paternal antigens. It has been suggested that in the aspect of differentiation of endometrial stromal cell, DCs play a positive role positive tropism, in proliferation, and local angiogenesis [18].

They are considered major regulators of the immune response, augmenting T cell-mediated immunity, and stimulating regulatory T cell induction. It is suggested that decidual DCs may also play a crucial role in the etiology of RSA. Any disturbance in their distribution, maturation state, or function might have a negative impact on pregnancy outcome, leading to adverse pregnancy outcomes [19].

In recent human studies, the following findings have been demonstrated: [1-4,25-30].

(1) Compared with the control group, the levels of myeloid DCs (MDCs), and CD86+ DCs in the RSA group were increased significantly, and CD200 expression on peripheral blood DCs was significantly lower in the RSA group;

(2) An elevated number of mature DCs and a decreased quantity of immature DCs may be associated with RSA;

(3) And compared with controls, ILT4+ DCs in the peripheral blood and endometrium were decreased in women with RSA [1,3,16].

Myeloid-derived suppressor cells

Myeloid-Derived Suppressor Cells (MDSCs) have emerged as a new immune regulator at the maternal-fetal interface. They participate in regulating other immune cells, especially on T cells, by suppressing their activities. We have two categories based on phenotypes: MDSCs (MO-MDSCs) and granulocytic MDSCs (GR-MDSCs). Recent studies have shown that GR-MDSCs generally accumulate at the maternal-fetal immune interface, and that their immunomodulatory properties may be significant for fetal-maternal tolerance In one study, researchers demonstrated that GR-MDSCs accumulated in the human placenta in healthy pregnancies, while they were remarkably diminished in patients suffering spontaneous abortion [11,15-20]. MDSCs are likely to function in RSA by regulating hypoxia-inducible factor 1α (HIF-1α). Previous research has also shown

that HIF-1α expression was lower in the missed abortion group than in the elective abortion group. Furthermore, scientists have extensively investigated the relationship between HIF-1α, MDSCs, and RSA, and recent research provides a reasonable explanation for the above phenomena.

Myeloid cells with deficient HIF-1α cause a diminishing accumulation of MDSCs, diminish the suppressive activity of MDSCs, increase the apoptotic rates of MDSCs, and enhance the abortion rate [1,31,32]. It is also known that MDSCs are myeloid cells with suppressive activity on other immune cells. Therefore, the alteration of the number and function of MDSCs has a negative influence on fetal-maternal immune tolerance. Furthermore, research clearly suggests that in Early Miscarriage (EM) patients, the decline in G-MDSCs is related to a decline in Estrogen (E2) and Progesterone (P4).

Women suffering from EM also generally experience poor endometrial receptivity, due to the downregulation of ER-α and contravariant expression of caspase-3 in endometrium decidua.

Neovascularization is crucial for decidualization and establishment of the placenta. Previous research has reported that MDSCs are associated with the progression of neovascularization [2,33]. They facilitate nonimmune reactions such as angiogenesis by secreting the key pro-angiogenesis inducer VEGF during pregnancy. Thus, we speculated that in RSA patients, the reduction of GR-MDSCs might lead to deovascularization disorder and embryo loss. A study confirmed this speculation, demonstrating that higher early miscarriage incidence is associated with a decrease in suppressive monocyte levels in the peripheral blood and endometrium of pregnant mice and women [3,34]. Immune cells always form an interactive network rather than being isolated in the immune system. For example, pregnancy loss as a possible result of myeloid-derived suppressor cell depletion is associated with the upregulation of decidual NK cell cytotoxicity [6,35]. Meanwhile, a remarkable feature of a successful pregnancy is the higher frequency of non-cytotoxic NK cells and lower number of cytotoxic NK cells present at the maternal-fetal interface [6,3]. Some studies show that MDSCs could not only suppress DC and T cell maturation but also supported uNK cells and resting macrophage development. It has also been documented that MDSCs can induce Foxp3+ T regulatory (Treg) cells by activating TGF-β via the TGF-β/β-catenin signaling pathway [6,4]. The proportion of uNK cells and Treg cells was therefore significantly upregulated, revealing that as a new immunosuppressive network system, the MDSCs-NK-Treg axis plays a complex and crucial role in regulating fetal-maternal immune tolerance. MDSC-tolerogenic dendritic cells and Treg cells play a crucial role in supporting normal pregnancy and placenta formation, and may represent a new network system in maternal-fetal immunity [1-6].

Another study has shown that MDSCs not only suppressed T cells via Reactive Oxygen Species (ROS) production but were also capable of inducing a shift toward Th2 cell subtypes in a cell-cell contact manner [6]. Moreover, these cells could reduce the presentation of L-selectin on immature T cells, inhibiting their trafficking toward lymph nodes and sustaining fetal-maternal tolerance Placental GR-MDSCs play a negative regulatory role in T cell responses by expressing arginase I and producing ROS [1,2,35]. In fact, GR-MDSCs can be sensitized at the immune interface between mother and embryo through interaction with trophoblasts. Moreover, GR-MDSCs isolated from placenta polarized CD4+ T cells toward a Th2 cytokine response. As mentioned above, due to the importance of MDSCs in pregnancy, their absence or dysregulation may cause complications [38,39].

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