War and Peace at the Feto-Placental Front Line: Recurrent Spontaneous Abortion

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Implantation is an event depending on several steps. The basic features of the fetal-maternal communication system of human pregnancy comprise two arms (placental and paracrine). The villous trophoblasts are the fetal tissue of the anatomic interface of the placental arm, while the fetal membranes are the fetal tissues of the anatomic interface of the paracrine arm of this system. A communication link is established by way of the placental arm: maternal blood directly bathes the villous trophoblasts; fetal blood is contained in fetal capillaries that traverse the intravillous space. At every step, there is a continuous embryo-uterus interaction. The discovery of the implantation window and emergence of the concept of uterine receptivity led to the intriguing idea that cytokines could be central to such a process [1].

During apposition/adhesion, the induction of adhesion molecules and the proper ligands are critical steps. Hence, it is essential that the expression of receptors/ligands at the cell surface of the embryo and uterus coincide. Interleukins (IL) are involved and hormonal regulation plays a major role in both the uterus and the embryo. Adhesion molecules are also modulated. Subsequently, invasion-penetration occurs, and at this step several enzymes are involved, especially matrix metalloproteases, counterbalanced by their inhibitors. In normal pregnancy, the maternal immunological response against trophoblast antigens, concomitant with a transient depression of maternal cell-mediated immunity to protect semi-allogenic embryo from rejection, is the predominant mechanism for a high live birth rate.

Recurrent spontaneous abortion (RSA) is defined as two or more consecutive spontaneous abortions, a heterogeneous condition (with numerous causes and clinical presentations) that may occur at any stage of pregnancy [2]. Mechanisms of RSA involve immune mediated pathways including the presence of a predominant T helper (Th)1-type immunity during pregnancy, a decrease in T regulatory cells and an increase in natural killer (NK) cells. These phenomena can occur locally (at the site of implantation) and are often reflected in the peripheral blood. The interaction between human leukocyte antigen molecules regulate NK cells activity at the maternal-fetal interface. Two main populations have been suggested, NK1 and NK2. The peripheral NK cells (PNKs) cytokine repertoire comprises mainly type 1 cytokines, such as interferon-gamma (IFNγ) and tumor necrosis factor-alpha (TNFα), although proper stimuli can induce production of type 2 cytokines such as IL-4, IL-5 and IL-13 [3]. Even more intriguing, NK cells have long been suspected as the cause of RSA since the original report by Aoki and colleagues [4]. In RSA, increased numbers and killing activity of NK cells in the peripheral blood predict the likelihood of another miscarriage and are considered a causal and prognostic factor for infertility, and miscarriage. Thus, NK cells may also play a key role in immunological infertility and in RSA if the concentrations are too high. In RSA, the creation of an imbalance in Th1-Th2 response, resulting in a prevalent Th1 cytokine environment in the periphery, may lead to NK cell activation and proliferation, which could result in migration of cytotoxic NK cells into the uterus and, in turn, contribute to mechanisms involved in miscarriage [5]. Alternatively, the local endometrial immune assessment may be disrupted at various levels, causing defects in homing of the proper NK population to the uterus, local production of cytokines and hormones such as IL-15 and prolactin, and impairment of more downstream events such as production of immunoregulatory factors by uterine NK cells. Disruption at any of these levels may alter the ability of the uterine NK cell population to perform its normal functions and may result in an unsuccessful pregnancy [6].

NK AND ANTIPHOSPHOLIPID ANTIBODIES (APL)

APL are found in approximately 5–17% of the general population but are more frequent in patients with RSA [3]. An increased number of NK cells correlate with reduced gestational age at abortion in patients with APS-RSA. NK cells might precipitate damage initiated by aPL or they might cause pathology in RSA independent of aPL, contributing to RSA

in patients with APS. APS is an autoimmune disease characterized by the presence of one or more laboratory findings of APL and at least one clinical manifestation in addition to deep venous and/or arterial thrombosis and/or pregnancy disease comprising RSA, with or without thrombocytopenia The association between APS and RSA is well known, such that RSA represents one of the clinical diagnostic criteria for APS.

The risk of pregnancy loss in women with APS is higher from the 10th gestational week (GW) onward (fetal period). The Sapporo criteria and the revised criteria for APS underline this situation by considering only patients with one or more unexplained fetal loss (of a morphologically normal fetus) beyond the 10th GW, or three or more unexplained consecutive spontaneous abortions before the 10th GW.

A number of controversies plague the current understanding of APS and RSA; thus several authors have reviewed the role of APS and specifically of APL in RSA and stressed the existence of different subclasses of clinical subsets of RSA in APS patients. Indeed, intrinsic to the definition of APS is a dichotomy regarding patients who have multiple (> 3) abortions within the first 10 GWs and those who have at least one abortion beyond the 10th GW.

Striking evidence of how NK cells behave as pathogenic effectors in RSA comes from a recent study that suggested the possible role of NK cells in the pathogenesis of abortive events in a subpopulation of APS-RSA patients, previously explained in terms of autoimmune specific reactions (APL-mediated).

aPL may cause pregnancy loss via many mechanisms such as thrombosis in decidual vessels, platelet activation, increased expression of adhesion molecules on endometrial cells, and inhibition of anticoagulants. Furthermore, aPL inhibit human chorionic gonadotropin secretion by trophoblast cells, prevent the metalloprotease urokinase from binding to receptors on the trophoblast and inhibit prostaglandin synthesis by decidual cells (decidualization), activated placental complement NK cells, and increase of TNFα, IL-1b and IL-6 [7].

NK, THYROID AND APL

Anti-thyroid antibodies and aPL are associated with reduced fertility, miscarriage and preterm delivery, but the precise mechanisms by which thyroid antibodies as well as those against other tissues are suppressed during pregnancy and often exacerbate after delivery remain obscure. Presumably, the rapid reduction in immune suppressor functions after delivery leads to the reestablishment and/or exacerbation of these conditions. Subclinical hypothyroidism of the mother may impair the course of pregnancy and may disturb the normal development of the fetus [8,9]. It usually originates from an underlying autoimmunity, the most common cause of thyroid dysfunction in pregnancy. Thyroid-stimulating hormone may act as a direct stimulator of the immune response, and triiodothyronine and thyroxine act on migration and proliferation of dendritic cells, NK cells and T cells. Previous studies suggested that the measure of peripheral blood NK cell percentage was a reliable predictor of pregnancy outcome in women with infertility and RSA rather than the measure of NK cell activity. All these data support the recommendation of assessing peripheral blood NK cell percentage in the context of female reproductive failure since it may enhance treatment outcome by delineating the underlying etiology [10].

CONCLUSIONS

The interactions between NK cell and other autoimmune factors, such as aPS and thyroid, may be associated with impaired pregnancy, and the modulation in the number of circulating NK cells is most likely a primary event rather than an active inflammation/drug administration consequence during an inflammatory/autoimmune process. Thus, NK cells are key players in the pathogenesis of RSA. The role of NK cells at different anatomic sites as well as the role of genetic factors, especially in terms of response to different stimuli from the local microenvironment to which NK cells home and become activated, should be further investigated.

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