

Natural killer cells in obstetric antiphospholipid syndrome

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Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombotic or obstetric events caused by persistent antiphospholipid antibodies (aPLs), namely lupus anticoagulant, anticardiolipin antibodies, or anti- β_2 glycoprotein I (anti- β_2 GPI) antibodies.^[1] The main target antigen in APS is β_2 GPI, through which aPL binds to the cell membrane and subsequently activates membrane receptors and downstream signal transducers. This may activate natural killer (NK) cells, leading to obstetric complications.

In the mother, NK cells and cytokines together produce immune tolerance, enabling the embryo to successfully evade the mother's immune system. In addition, uterine NK (uNK) cells are involved in trophoblast cell invasion and spiral artery remodeling, secreting cytokines that regulate immune balance at the maternal–fetal interface. Changes in the number and function of NK cells and the imbalance between NK cells and other immune cells may lead to pathological pregnancy, including preeclampsia and recurrent pregnancy loss (RPL).

Immune disorders caused by NK cells in APS are closely related to adverse obstetric events, but the underlying mechanisms have not been fully elucidated. This paper reviewed the relationship between NK cells and APS pathological pregnancy to provide a basis for the treatment of patients.

Three possible pathways are recognized for the origin of uNK cells. In the first pathway, local microenvironments in the human decidua such as galactoselectin 9/T cell immunoglobulin and mucin domain 3 signaling induce peripheral blood NK (pNK) cells to transform into an uNK-like phenotype. The second pathway may be the migration of CD16 + pNK cells into the uterine tissue, altering the uNK phenotype under the influence of factors

such as transforming growth factor- β (TGF- β). In addition, when co-cultured with decidual stromal cells *in vitro*, IL-15 stimulates CD34 + CD122 + CD127 + hematopoietic progenitors to differentiate into uNK cells.

Based on function, NK cells contain two types of receptors, activating killer receptors (AKRs) and inhibiting killer receptors (IKRs). According to their structure, receptors can be divided into killer cell immunoglobulin-like receptors (KIRs), killer cell lectin-like receptors (KLRs), and natural cytotoxic receptors (NCR). KIR, two Ig domains, and long cytoplasmic tail 1 (KIR2DL1), 2DL2, and 2DL3 are IKRs that bind with HLA-C to regulate the cytotoxicity of decidual NK cells [Figure 1A]. KIR, two Ig domains, and short cytoplasmic tail 1 (KIR2DS1) also interacts with HLA-C [Figure 1B] and activates downstream by combining with adaptor protein DAP12.^[2] The immune receptor tyrosine-based activator (ITAM) in DAP12 activates NK cells and produces pro-inflammatory cytokines. NKG2 is a member of the KLR family, and NKG2D is an AKR that activates NK cells. NKG2A is an IKR that inhibits excessive NK cell activation, and it consists of three type I transmembrane receptors, NKp46, NKp44, and NKp30. NCR is an AKR-type receptor that lacks ITAM in cells and can activate signals via the three aforementioned receptors,^[3] mediating the toxic effects of uNK cells. During pregnancy, optimal production of cytokines and growth factors (such as vascular endothelial-derived growth factor) occurs when the AKRs and IKRs of uNK cells are in homeostasis, enhancing maternal immune tolerance of embryonic cells [Figure 1A]. When the regulation of uNK cells at the maternal–fetal interface is unbalanced, excess harmful cytokines are produced, leading to abortion [Figure 1B].

Through their roles in trophoblast invasion and spiral artery remodeling during early pregnancy, uNK cells

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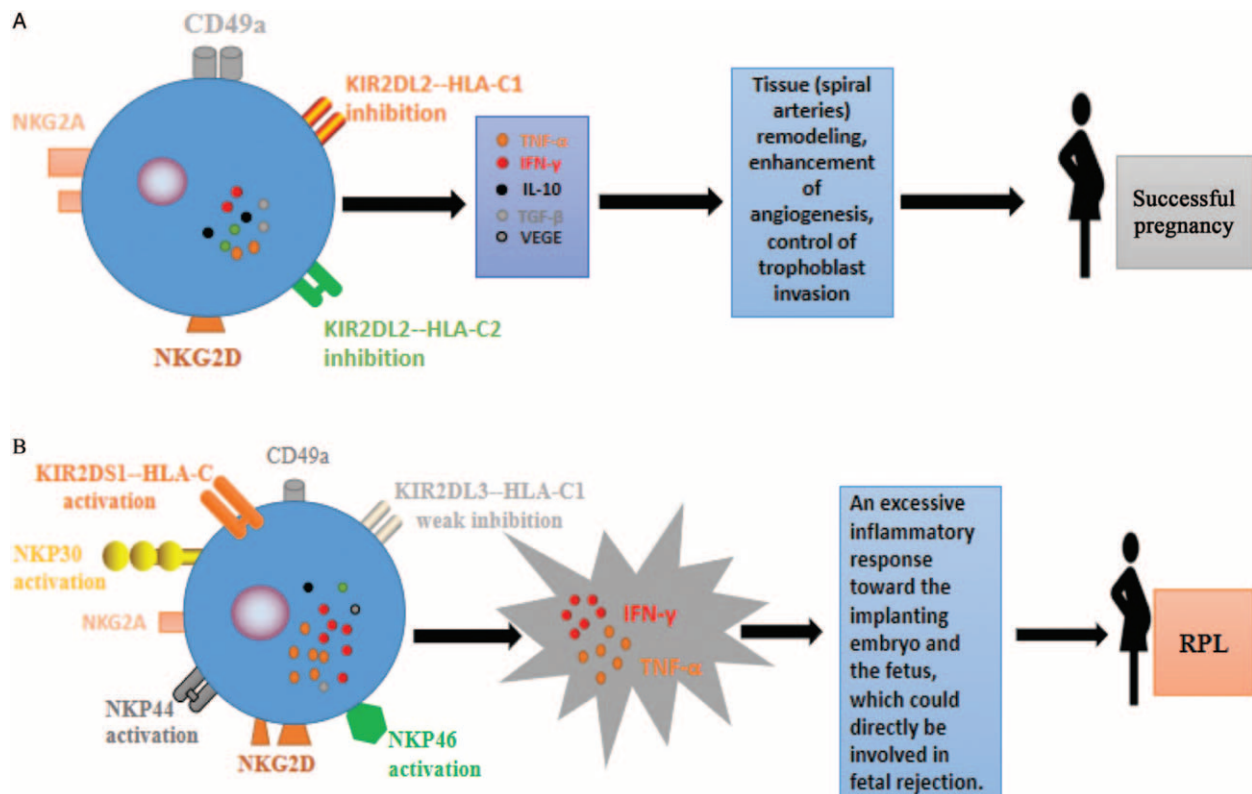


Figure 1: (A) uNK cells of healthy fertile female patients. (B) uNK cells of patients with RPL. IFN- γ : Interferon- γ ; IL-10: Interleukin-10; RPL: Recurrent pregnancy loss; TGF- β : Transforming growth factor- β ; TNF- α : Tumor necrosis factor- α ; uNK: Uterine NK; VEGF: Vascular endothelial-derived growth factor.

promote embryonic development. TGF- β and interleukin-10 secreted by uNK cells are associated with promoting trophoblast cell invasion, evading maternal attack on the fetus, and enhancing angiogenesis [Figure 1A]. The absence of invasive extravascular trophoblasts in early-development spiral arteries suggests that uNK cells play an important role in the reconstruction of spiral arteries. As a result, uNK cells transform spiral arteries into highly dilated blood vessels, ensuring low-pressure blood flow to the placenta and developing fetus [Figure 1A]. In addition, CD49a + Eomes + uNK cells produce growth factors that promote embryonic development before placenta establishment in humans and mice.

Normal development of a fetus can be contributed to the normal number and percentage of pNK and uNK cells during pregnancy. Current studies on pNK cells in patients with RPL have yielded conflicting results. Previous studies have found no significant difference in the number of pNK cells in RPL patients. However, Kuon *et al*^[4] found that the absolute number and percentage of pNK cells in RPL patients were higher than those in the healthy control group. The different results of studies on pNK cells in RPL women may be due to differences in experimental methods and different periods of pregnancy. Zhang *et al*^[5] linked the increased number and percentage of uNK cells to preeclampsia and fetal growth restriction. These results suggest that the number and percentage of pNK and uNK cells should be maintained within a certain range to ensure normal embryonic development.

During normal pregnancy, NK cells play an important role in mediating immune tolerance and promoting embryonic growth. In APS patients, the imbalance between NK cells and other immune cells and their secreted cytokines may lead to maternal rejection of the fetus. Studies have shown that anti- β 2GPI antibodies inhibit trophoblastic cell autophagy, induce excessive activation of inflammasomes, and increase secretion of pro-inflammatory factor IL-1 β , thereby triggering excessive activation of the maternal and fetal interface inflammatory response.^[6] This may be the pathogenic mechanism of APS-induced RPL. In APS patients, β 2GPI polarizes helper T (Th) cells into Th17 cells and activates uNK cells in the placenta to produce interferon- γ and tumor necrosis factor- α (TNF- α), mediating their cytotoxic activity against target cells,^[7] which may damage placental endothelial cells and lead to the placental microthrombus formation. Excessive TNF α induces the proliferation of uNK cells and promotes their differentiation into cytotoxic lymphocyte-cytotoxic killer cells, leading to APS-RPL.

NK cells can adopt anti-trophoblast characteristics under specific conditions. For example, uNK cells, which are abnormally activated in mice in response to inflammation caused by bacterial endotoxins, target embryonic tissue and induce fetal absorption. The uNK cell-induced remodeling of uterine arteries and placental damage can be reversed by inhibiting uNK cells using NK cell antibodies (ie, by reducing the number of uNK cells and inhibiting Nkp46). In addition, low-dose rapamycin increased the number of uNK cells and decreased the

expression levels of NKG2D, NKP30, and NKP46 through autophagy in aborted NK cell-depleted mice, thus promoting embryo absorption in aborted mouse models.^[8] Therefore, the intervention in animal models indicates that the abnormal number and function of NK cells may be closely related to pathological pregnancy.

Abnormal numbers and functions of NK cells in patients with APS can lead to miscarriage. However, appropriate intervention can increase the success rate of pregnancies. Studies have shown that uNK cells are elevated in women with pathological pregnancy. Prednisone was confirmed to reduce uNK cell number^[9]; however, it did not improve pregnancy outcomes. In addition, the use of intravenous immunoglobulin (IVIG) can increase the live birth rate in patients with abortions. Ahmadi *et al*^[10] found that the percentage and cytotoxicity of NK cells in RPL patients treated with IVIG were significantly reduced and that the expression levels of KIR2DL1, KIR2DL2, and KIR2DL3 in NK cells were increased, while the expression levels of NKG2A and KIR2DS1 were significantly decreased, which promoted live birth rate in the IVIG group.

Successful pregnancy is the result of a complex confluence of factors. The interaction between NK cells and cytokines inhibits inflammation and aids to establish a balanced immune network at the maternal-fetal interface. Changes in the number of uNK cells, dysfunction, and proportional imbalance with other immune cells at the maternal-fetal interface may play a key role in APS-RPL. The specific signaling pathways and cytokines involved in NK cell immune regulation imbalance remain unclear; therefore, further studies are needed to provide effective immune or targeted therapy.

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Conflicts of interest

None.

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