

Research progress in the mechanism of action of NK cell-related receptors during recurrent spontaneous abortion

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Abstract: Recurrent spontaneous abortion (RSA) refers to multiple spontaneous abortions with the same sexual partner; In 2020, Chinese expert consensus suggested that it should be defined as the loss of the embryo or fetus before 28 weeks of gestation with the same sexual partner for two or more times in a row, including the biochemical pregnancy that occurred several times in a row. The pathogenesis of RSA is complex and diverse. At present, the pathogenesis factors have been widely recognized by the industry, including genetic factors, endocrine factors, anatomical abnormalities, infectious factors and immune factors. Among them, the role of immune factors such as T lymphocytes, dendritic cells and natural killer cells (NK) in the occurrence and development of RSA has attracted wide attention, especially NK cells. NK cells are an important part of human immune system. The specific surface molecules of Decidual natural killer cell (dNK) play an immunomodulatory role in the invasion of trophoblast cells and the remodeling of uterine spiral artery during pregnancy, which is particularly important in the early gestation period. The function of dNK cells is tightly regulated by a balance between activation and inhibition signals transmitted by the various family of receptors (NK cell receptors, NKRS) that DNK cells express. In this paper, the existing research progress of decidual NK cells on the mechanism of its receptors in the process of recurrent spontaneous abortion will be reviewed as follows.

Keywords: Recurrent spontaneous abortion; Decidual natural killer cells; Receptors

1. Introduction

Recurrent abortion (RSA) is one of the common pregnancy complications in obstetrics and gynecology, and also a common disease related to reproductive immunity in obstetrics and gynecology, which seriously threatens the physical and mental health of the majority of women. Although most of the pathogenesis of RSA has a clear etiology, there are still many triggers of RSA that have not been discovered clinically, most of which are thought to be related to immune abnormalities. During normal pregnancy, various immune cells and cytokines work together to develop an immune tolerance that allows the embryo to successfully evade the maternal immune system. Natural killer cells (NK cells) are the focus of immunologists in recent years. These cells play an important role in the process of recognizing and killing cells with abnormal differentiation, morphological changes and infection. During pregnancy, the number of decidual natural killer cells (dNK cells) continues to increase and maintain close contact with trophoblast cells, so the interaction between DNK cells and trophoblast cells at the mother-to-fetus interface can be regarded as the cellular basis of maternal immune tolerance to fetal isoantigen recognition and thus achieve fetal immune protection^[1]. Professor ElBadawy Omnia et al.^[2]from the School of Medicine of Assu University in Egypt found in their study on killer immunoglobulin-like receptors in peripheral blood of women with recurrent spontaneous abortion that NK cells could be subdivided into different subgroups according to the relative expression of CD16 and CD56, namely CD56dimCD16bright(low expression, CD16dim(high expression, low expression or no expression) were the two main subgroups of NK cells. CD56+ NK cells in peripheral blood accounted for 17.5%, and CD56+ NK cells in decidua accounted for 17.3%. CD56dim NK cells were higher than CD56bright NK cells in blood and decidua. As for the function of these cells, studies have found that

dNK cells can not only play an immunomodulatory role in the maternal fetal interface^[3], but also play a key role in the regulation of trophoblast invasion and vascular remodeling^[4, 5].

In the process of recognizing and killing target cells, these NK cells need to rely on the interaction of inhibitory receptors and activator receptors on the surface of NK cells with MHC molecules on the surface of target cells, so that the combination signals generated by the change of the balance between inhibitory signals and activator signals recognize abnormalities in vivo. NK cell surface receptors are abundant and diverse. These receptors and their ligands may play different regulatory roles in the pathogenesis of spontaneous abortion. NK cell surface receptors are mainly divided into two families: Immunoglobulin superfamily [including the killer immunoglobulin-like receptor (KIRs) family, natural cytotoxic receptor (NCR), and LIR(leukocyte IG-like receptor)/ILT(immunoglobulin like transcript)LIR receptors], C-type lectin family [CD94/NKGs and CD94/NKG2 receptors (natural killer genes), NKG2D receptors]^[6]. During pregnancy, they promote maternal acceptance of the embryo through various immunomodulatory mechanisms. Natural killer cell receptor (NKR) is a central regulator of NK cell activity^[7]. However, the specific regulatory mechanisms of various receptors have not been studied clearly. The following will review the research progress of the pathogenesis and regulation mechanism of receptors and ligands mentioned above in spontaneous abortion.

2. Killer immunoglobulin-like receptor(KIR)

Most of the receptors that regulate the activation and inhibition of dNK cell function belong to the highly polymorphic KIR(Killer immunoglobulin-like receptor) family. 3. Killer immunoglobulin-like receptors (KIRs), which recognize human leukocyte antigen Class HLA-I molecules, are particularly important for NK cell function. At the maternal fetal interface, only the echinotrophoblast (EVT) expresses selective class HLA-I molecules, while all other types of trophoblast cells have no HLA expression. Each pregnancy has a unique combination of KIR and HLA-I, which, combined with the fact that NK cells interact directly with the trophoblast, suggests that KIR and HLA may play a role in RSA^[8]. EVT expresses HLA-C, HLA-E and HLA-G^[9, 10]. If the interaction between KIR and its own HLA Class I molecules is suppressed, they will inhibit the activation of dNK cells, thus damaging trophoblast cells^[11, 12].

KIRs can be classified according to their structure and function. Each KIR molecule consists of two or three extracellular immunoglobulin-like domains (2D and 3D molecules, respectively), a transmembrane region, and a short (S) or long (L) intracellular tail^[11, 13]. KIR is expressed on a subpopulation of NK cells and may therefore affect the activation of this cell, either by inhibiting KIRs[with long (L) cytoplasmic tails -KIR2DL and KIR3DL- containing inhibitory motifs ITIMs based on immune receptor tyrosine], Either by activating KIRs (KIR2DS and KIR3DS, short (S) cytoplasmic tails have no signaling motifs but are related to the adaptor molecule DAP12 homodimer, which has activation motifs ITAMs based on the immune receptor tyrosine).

KIR receptors are transmembrane glycoproteins expressed on NK cells and T lymphocytes with characteristic immunoglobulin (Ig) -like domains on extracellular segments of NK cells associated with target cell surface ligand recognition. All KIR genes are encoded in the leukocyte receptor complex (LRC) of chromosome 19 (19q14.3)^[14]. LRC includes 15 genes of the KIR family. The genes encoding KIR are polymorphic. The two types of KIR haplotypes, A and B, can be defined by 15 genes of the KIR family^[11, 15]including KIR2DS1, KIR2DS2 KIR2DS3, KIR2DS4 KIR2DS5, KIR2DL1, KIR2DL2 / L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR3DL1, KIR3DL2, KIR3D, KIR3DL3 and KIR3D S1^[10, 16].

At present, Professor Su Ning and his team from the Affiliated People's Hospital of Zhengzhou University have conducted a study on the influence of KIR gene and HLA-C ligand on recurrent spontaneous abortion in Han population. This study detected KIR and HLA-C genes in 110 Han women with unexplained RSA and 105 healthy Han women to determine whether certain genotypes are more prone to abortion. The final results showed that, compared with the control group, the frequency of KIR3DL1 in RSA patients was significantly lower, and the frequency of 2DS1 gene was significantly higher, but there was no significant difference in the frequency of KIR gene and different KIR haplotypes between the two groups. The decrease of suppressor gene and the increase of activator gene may induce the activation of natural killer cells. Thus, the probability of fetal survival is reduced, leading to the occurrence of abortion^[17]. This study suggests that maternal KIR and HLA-C genes are associated with RSA in Chinese Han women, but the mechanism has not been further studied, which has certain enlightenment for our exploration of the mechanism of KIR receptor gene in the occurrence

of RSA.

3. Natural cytotoxicity receptors(NCR)

Natural cytotoxic receptors (NCR) are also subordinate to the immunoglobulin superfamily, including Natural Cytotoxic receptor-1, NCR1 (NKp46), natural cytotoxicity receptor-2 (NKp44), natural cytotoxicity receptor-3 (Natural Cytotoxicity receptor-1, NCR3 is NKp30)^[18]. These receptors play an important role in the recognition of target cells with little expression of major histocompatibility complex (MHC). NCR also has an immunoglobulin (Ig) -like domain in its extracellular part, which makes it a member of the immunoglobulin superfamily. Ligands recognized by this class of receptors include stress inducing proteins (ligands of NKG2D), viral proteins (such as hemagglutinin), pp65(ligands of NKp44, NKp46, and NKp30), and some unidentified tumor ligands^[19, 20].

Since NCRs lack the activation motif of immune receptor tyrosine (ITAM), they can only transmit activation signals to the cell through ITAM-related molecules^[21]. NKp46 and NKp30 can be expressed on both resting and activated NK cells, while NKp44 is only expressed on activated NK cells. NKp30 can be transcribed into different variants, among which NKp30a, NKp30b and NKp30c are the most abundant isomers, each of which has a different function. NKp30a and NKp30b transmit activation signals, while NKp30c transmit suppression signals; NCR1 and NCR2 were also transcribed into several isomers, but no functional differences of splicing variants were found in NCR1, and there were inhibitory isomers in NCR2^[22]. In addition, all three kinds of NCRs have been repeatedly shown to induce cytotoxic effect of uterine NK cells and cytokine production, but only NKp46 can induce cytotoxic effect of dNK cells^[23]. In addition, NKp30 can promote the secretion of cytokines, while NKp44 has inhibitory function in dNK cells^[22].

Professor Fukui Atsushi's team in Japan studied the expression of natural cytotoxic receptors and cytokines on endometrial natural killer cells in women with recurrent abortion or implantation failure. The expression of NCR (NKp46, NKp44 and NKp30) and the generation of NK cells in the endometrium of women with recurrent pregnancy loss (RPL) were studied. The expression of NCR (NKp46, NKp44 and NKp30) in dNK cells was detected by flow cytometry. Medium dNK cells were collected from 34 women with implantation failure and 74 control groups. The expression of NCR in peripheral blood of pregnant women was analyzed. The results showed that the expression of NCR and cytokine production were changed, especially the expression of NKp46 in dNK cells was decreased, which suggested that there might be abnormal regulation of NK cells in women with recurrent abortion^[24]. However, this study only explored the expression of several NCR receptors in RSA patients, and did not conduct in-depth research on the specific mechanism.

NKp46 can be further subdivided into NKp46dim and NKp46bright. Chuxian Mai^[25] et al. studied the role of NKp46 receptors in determining reproductive outcome. By collecting the endometrium of aborted women, the endometrium was divided into pregnancy group and pregnancy failure group according to the results of pregnancy reaction test. NKp46 receptor and other activating or inhibiting receptors expressed on NK cells and intracellular factors produced by NK cells were analyzed by multicolor flow cytometry. It was found that NKp46 receptors play different roles in reproduction according to different fluorescence intensities associated with NK cells, that is, NKp46dim NK cells are involved in cell killing, while NKp46bright NK cells are involved in cytokine production, suggesting that NKp46 may be a predictive marker for observing embryo tolerance conditions. It suggests that this receptor plays an important role in the pathogenesis of RSA. However, this study did not conduct in-depth discussion on the interaction between NK cell receptors and their respective HLA antigens in RSA patients, so it has certain implications for our future research on the interaction between NK cell receptors and their respective HLA antigens in RSA patients.

4. Leukocyte immunoglobulin receptor(ILT)

Some members of the LILR family of leukocyte immunoglobulin-like receptors (LILR), also known as ILTs (Immunoglobulin-like transcripts), which are present in the human placenta; LILRB1 (B member 1 of the leukocyte immunoglobulin like receptor family, i.e. ILT2) was mainly found on stromal cells, while LILRB2 (B member 1 of the leukocyte immunoglobulin like receptor family, i.e. ILT4) was also found around the vessels of the smooth muscle layer in addition to stromal cells. Leukocyte immunoglobulin like receptor (LIR) is a type I transmembrane glycoprotein containing the

extracellular ligand-binding immunoglobulin like domain and the intracellular immunoreceptor tyrosine inhibitory motif (ITIM), and is therefore classified as an immunosuppressive receptor^[26]. These receptors are similar to KIR, encoded on chromosome 19 in the q13 region, and LILRA (activating) and LILRB (inhibiting) receptors are more widely distributed than KIR.

HLA-G belongs to non-classical human leukocyte antigen (HLA) class I, encoded by the HLA-G gene, and was originally found in trophoblast cells. Trophoblast cells belong to deciduar invading cells, which are allografts to the mother. As we can see from the above, HLA-G is highly expressed in trophoblast cells, which can directly inhibit the killing effect of NK cells, so as to protect fetal cells from the attack of NK cells^[27]. The binding of HLA-G tetramer was found to be mediated by ILT receptor, mainly by ILT4, with a certain contribution from ILT2, but only when the latter was expressed at a high level. The expression rate of ILT2 in all female decidua NK cells was 20-25%, and both ILT2 and ILT4 were present in all decidua macrophages. When ILT2 and ILT4 bind to HLA-G on trophoblast cells, the inhibitory function of ILT2 and ILT4 may counteract the activation signal of KIR2DL4. LILRB1 contains a tyrosine immune receptor switch motif in the cytoplasmic region, which can act as both an activating receptor and an inhibiting function. LILRB1 binds to HLAG more strongly than classical HLA Class I molecules, and HLA-G dimer induces LILRB1 signaling more effectively than monomer form^[28].

In recent years, there are few studies on the expression and effect of the inhibitory receptor LIR/ILT and its ligand HLA-G on the surface of NK cells in the decidua at the maternal fetal interface in recurrent abortion. Therefore, the in-depth exploration of the relationship between the mother-to-fetus interface can also be a new direction to explore the mechanism of abortion.

5. CD94/NKG2A

CD94/NKG2A is a receptor that exists on natural killer cells (NK) and some T cells. CD94 is covalently bonded to other members of the NKG2 family of molecules. Both molecules are glycosylated members of the C-type lectin superfamily. The CD94/NKG2A receptor is a peptide molecule specifically derived from HLA-E and a specific MHC Class I molecular signal sequence. The location of the signal sequence derived peptides is critical in determining whether HLA-E/ peptide complexes are resistant to NK cell-mediated cleavage^[29].

In view of this, Brooks et al.^[30] from the National Institute of Allergy and Infectious Diseases of the United States confirmed the specific interaction between CD94/NKG2A and HLA-E, and demonstrated that this interaction depends on the binding of HLA-E to the above derived peptides. In addition, by functional analysis of CD94/NKG2A+ NK cells, no interaction between CD94/NKG2A and classical HLA Class I molecules was observed. They also evaluated the function of HLA-E-related peptides in the interaction between HLA-E and CD94/NKG2A. It was found that all class I lead peptides needed to bind to HLA-E and were recognized by CD94/NKG2A. It can be said that HLA-E's specific recognition of CD94/NKG2A is controlled by peptides at two levels; First, the peptide must stabilize HLA-E and promote its expression on the cell surface. In addition, the HLA-E/ peptide complex must form a ligand for CD94/NKG2A^[29].

As the surface receptors of NK cells exert cytotoxic effects mainly through their inhibitory receptors, and CD94/NKG2A, as such receptors, begin to be synthesized and expressed slowly at the beginning of the development of NK cells in vivo, interleukin-15, together with other cytokines, can promote the differentiation of progenitor cells and enhance the expression of CD94^[31]. During pregnancy, NK cells are essential for the formation of the placenta, a key organ that controls the supply of oxygen and nutrients needed by the growing fetus. Instead of attacking mismatched fetuses and their placentas, uterine NK cells help local blood vessels tolerate the changes needed to nourish the fetus. Control of NK cell function depends on the interaction between class HLA-I and inhibitory NK cell receptors^[32]. Human beings first evolved the interaction between HLA-E and CD94/NKG2A. Hla-e acts as a ligand for CD94/NKG2A on the surface of trophoblast cells. Driven by CD94/NKG2A inhibitory receptor and HLA, uterine NK cells promote them to transmit these key functions at the mother-to-fetus interface. Secondly, multiple interactions of HLA-A, -B, and -C with killer cell immunoglobulin-like receptors (KIR) were gradually established^[33].

6. NKG2D

The NKG2D immune receptor is expressed in most NK cells^[34]. The expression of NKG2D in dNK

cells decreased during the first trimester, but increased during the second trimester^[35]. NKG2D belongs to the C-type lectin receptor family, and its ligands are MICA and MICB, which are MHC class I homologs^[36]. Human stress-induced interaction of MHC Class I chain (MIC) related proteins A and B (MICA/B) with their homologous receptor NKG2D is an immune escape mechanism. The MIC molecule is the ligand of NKG2D, a receptor activated by NK cells expressed on the surface of human NK cells. The MIC molecule can act as a cellular stress signal *in vivo* and trigger a series of immune effect functions. The mutual recognition and cross-linking of the MIC molecule and the NKG2D receptor enable immune cells to recognize and attack the emerging stress cells externally. No MHC Class I expression or antigen recognition is required; Therefore, it can be said that the MIC/NKG2D interaction is an effective immune surveillance mechanism^[37].

In addition, the activation of phosphatidylinositol-3-kinase (PIK3) is required for the formation of NKG2D immune synapses; In human NK cells, NKG2D receptor stimulation signals can be mediated by related DAP10 adaptors. NKG2D itself is involved in stimulating NK cells to form immune synapses and can recruit NKG2D to central synapses. In this process, the binding site of PIK3 is essential. It is also sufficient to recruit DAP10 to the immune synaptic site of NK cells prior to stimulation of new signal transmission^[38]. During female pregnancy, maternal immune tolerance to the fetus is closely related to many immunosuppressive factors produced by the placenta. Placenta-derived exosomes appear in maternal immune tolerance as a new immune regulatory factor. Exosomes are membrane-like nano-sized vesicles with well-defined morphology, secreted by the fusion of endosomal polycystic bodies (MVB) with the plasma membrane. Exocrine bodies transmit cell-to-cell contact by proxy. During contact, exosomes transfer molecules associated with them, giving them new properties and reprogramming recipient cells. Human placental trophoblast cells are able to continuously secrete exosomes constitutionally throughout pregnancy, and these exosomes are transmitted directly in the maternal blood around the placental chorionic membrane. Exert its immunosuppressive function^[39, 40].

MHC Class I chain associated (MIC) proteins A and B are expressed by the placenta during pregnancy, sorted in endosomal polycysts within syncytial trophoblast cells, and released by MIC-carrying exosomes^[40]. The maternal immune response of NKG2D to the fetus at the maternal-fetal interface may lead to repeated abortion, and NK cells accumulate at the maternal-fetal interface and play an important role during pregnancy. On the surface of DNK cells, NKG2D ligands activate NK cells by binding to corresponding receptors. During normal pregnancy, syncytial trophoblast cells secrete soluble NKG2D ligands (MICA and MICB) into serum, interfering with NKG2D-mediated maternal anti-fetal immune response. These decreased levels of soluble NKG2D ligand are associated with increased levels of NKG2D in NK cells, and this process may be involved in the pathogenesis of RSA^[41].

Hizem Sondes et al.^[42] conducted an experimental investigation on the gene polymorphism of NK cell receptor NKG2D and its ligand MICA in recurrent abortion, aiming to explore the possible relationship between NKG receptor gene polymorphism and MHC Class I chain associated protein A (MICA) gene polymorphism and RSA. Allele identification was used to detect 7 single nucleotide polymorphisms (rs1049174, rs2255336, rs2617160, rs2617161, rs2246809, rs2617169, and rs2617170) and 1 of NKG2A gene in patients and control women One single nucleotide polymorphism (rs1983526) and one single nucleotide polymorphism (MICA129) of the MICA gene; The results also suggest that NKG2D gene polymorphism may affect the pregnancy success rate of women. According to literature review, it is found that current studies on NKG2D in obstetrics and gynecology mostly focus on the immune level of ovarian tumor and viral infection, while there are few studies on its role in the maternal fetal interface of recurrent spontaneous abortion. This can also provide a new direction for our research on the immune mechanism of spontaneous abortion.

7. Conclusion

The increase in the number of NK cells and their cell membrane surface receptors before and after conception in women with recurrent spontaneous abortion is an important clinical problem. Decidual NK cells are considered to be the main cell population of the embryo "rejected" by the mother (alloimmune abortion). According to the existing studies on the surface receptors of decidual NK cells, embryo rejection may be the result of the defect of the NK allorecognition system. In other words, the toxicity of decidual NK cells in patients with spontaneous abortion is closely related to the lack of epitope-matching between various receptors on the surface of NK cells at the maternal and fetal interface and their related ligand. The activation of decidual NK cells is not blocked through the weakened or missing of the matching between receptors and ligand, so that the killing effect of NK

cells plays a dominant role, enabling them to obtain the killing license. Allowing NK cells to destroy the trophoblast without hindrance, leading to pregnancy failure. The complexity of the immune recognition system associated with NK cells makes it difficult for researchers to analyze its effect on pregnancy outcome. Therefore, the research of immune or immune genetic mechanism in reproductive process is still a challenge for us to study natural abortion. Increase the research of KIR/HLA-C complex, several subtypes of NCR, NKp44/NKp46/NKp30, LIR/ILT/HLA-G complex, CD94/NKG2A complex and NKG2D. It is expected to contribute to a better understanding of the pregnancy model in which the immune receptors and ligands on the surface of NK cells at the maternal fetal interface play a role in mutual recognition, contribute to the etiological analysis of patients with unexplained spontaneous abortion, and even provide ideas for the treatment of patients with unexplained spontaneous abortion in the future, such as the study of targeted therapeutic drugs for related receptors and/or their related ligands^[1].

References

- [1] Croy BA., He H, Esadeg S. (2003) *Uterine natural killer cells: insights into their cellular and molecular biology from mouse modelling*. *Reproduction*, 2, 149-160.
- [2] EB ASH., AMA., (2020) *Concordance between peripheral and decidual NK cell subsets and killer immunoglobulin-like receptors in women with recurrent spontaneous miscarriages*. *J reprod immunol*, 1, 103-130.
- [3] Xie M., Li Y., Meng YZ. (2022) *Uterine Natural Killer Cells: a rising star in human pregnancy regulation*. *Front Immunol*, 13, 918550.
- [4] H Lu., L Jin., H Huang. (2020) *Trophoblast-derived CXCL12 promotes CD56(bright) CD82(-) CD29(+) NK cell enrichment in the decidua*. *Am J Reprod Immunol*, 83, e13203.
- [5] Ran GH., Lin YQ., Tian L. (2022) *Natural killer cell homing and trafficking in tissues and tumors: from biology to application*. *Signal Transduct Target Ther*, 7, 205-205.
- [6] Varla-Leftherioti M., Keramitsoglou T. (2016) *Natural killer (NK) cell receptors and their role in pregnancy and abortion*. *J Immunobiol*, 1, 1-6.
- [7] Feyaerts D., Kuret T., Van Cranenbroek B. (2018) *Endometrial natural killer (NK) cells reveal a tissue-specific receptor repertoire*. *Hum Reprod*, 33, 441-451.
- [8] Colucci F. (2017) *The role of KIR and HLA interactions in pregnancy complications*. *Immunogenetics*, 69, 557-565.
- [9] Gao F., Ye Y., Gao Y. (2020) *Influence of KIR and NK Cell Reconstitution in the Outcomes of Hematopoietic Stem Cell Transplantation*. *Front Immunol*, 11, 2022-2022.
- [10] Diaz-Pena R., de Los S M., Lucia A. (2019) *Understanding the role of killer cell immunoglobulin-like receptors in pregnancy complications*. *J Assist Reprod Genet*, 36, 827-835.
- [11] Akbari S., Shahsavari F., Karami R. (2020) *Recurrent Spontaneous Abortion (RSA) and Maternal KIR Genes: A Comprehensive Meta-Analysis*. *JBRA Assist Reprod*, 24, 197-213.
- [12] Kniotek M., Roszczyk A., Zych M. (2021) *Differences in the Expression of KIR, ILT Inhibitory Receptors, and VEGF Production in the Induced Decidual NK Cell Cultures of Fertile and RPL Women*. *Biomed Res Int*, 5, 1-10.
- [13] Liu Y., Gao S., Zhao Y. (2021) *Decidual Natural Killer Cells: A Good Nanny at the Maternal-Fetal Interface During Early Pregnancy*. *Front Immunol*, 12, 151-168.
- [14] Deng Z., Zhen J., Harrison G F. (2021) *Adaptive Admixture of HLA class I Allotypes Enhanced Genetically Determined Strength of Natural Killer Cells in East Asians*. *Molecular biology and evolution*, 6, 2582-2596.
- [15] Debska-Zielkowska J., Moszkowska G., Zielinski M. (2021) *KIR Receptors as Key Regulators of NK Cells Activity in Health and Disease*. *Cells*, 10, 1777-1777.
- [16] Su N., Wang H., Zhang B. (2018) *Maternal natural killer cell immunoglobulin receptor genes and human leukocyte antigen-C ligands influence recurrent spontaneous abortion in the Han Chinese population*. *Exp Ther Med*, 1, 327-337.
- [17] Ning S., Hongdan W., Bowei Z. (2018) *Maternal natural killer cell immunoglobulin receptor genes and human leukocyte antigen-C ligands influence recurrent spontaneous abortion in the Han Chinese population*. *Experimental and therapeutic medicine*, 15, 327-337.
- [18] Hui Yihua, Wang Haina., Su Wen. (2020) *Research progress on the expression profile and function of Natural killer (NK) cell surface receptors*. *Journal of Cell and Molecular Immunology*, 8, 740-744.
- [19] Shmeleva EV., Colucci F. (2021) *Maternal natural killer cells at the intersection between reproduction and mucosal immunity*. *Mucosal Immunol*, 5, 991-1005.
- [20] Hanna J., Goldman-Wohl D., Hamani Y. (2006) *Decidual NK cells regulate key developmental processes at the human fetal-maternal interface*. *Nature Medicine*, 12, 1065-1074.

- [21] Luczo JM., Ronzulli SL., Tompkins SM. (2021) *Influenza A Virus Hemagglutinin and Other Pathogen Glycoprotein Interactions with NK Cell Natural Cytotoxicity Receptors NKp46, NKp44, and NKp30*. *Viruses*, 13, 156.
- [22] Siewiera J., Gouilly J., Hocine H. (2015) *Natural cytotoxicity receptor splice variants orchestrate the distinct functions of human natural killer cell subtypes[J]*. *Nature Communications*, 6, 10183.
- [23] Yamamoto M., Fukui A., Mai C. (2022) *Evaluation of NKp46 expression and cytokine production of decidual NK cells in women with recurrent pregnancy loss*. *Reprod Med Biol*, 21, e12478-e12478.
- [24] Atsushi F., Ayano F., Rie F. (2017) *Expression of natural cytotoxicity receptors and cytokine production on endometrial natural killer cells in women with recurrent pregnancy loss or implantation failure, and the expression of natural cytotoxicity receptors on peripheral blood natural killer cells in pregnant women with a history of recurrent pregnancy loss*. *J Obstet Gynaecol Res*, 8, 1678-1686.
- [25] Mai C., Fukui A., Takeyama R. (2021) *NK cells that differ in expression of NKp46 might play different roles in endometrium*. *J Reprod Immunol*, 9, 103367-103367.
- [26] Feifei Z., Junke Z., Xunlei K. (2015) *Inhibitory leukocyte immunoglobulin-like receptors in cancer development*. *Sci China Life Sci*, 11, 1216-1225.
- [27] Xu X., Zhou Y., Wei H. (2020) *Roles of HLA-G in the Maternal-Fetal Immune Microenvironment*. *Front Immunol*, 11, 592010-592010.
- [28] Nowak I., Wilczyńska K., Wilczyński J R. (2017) *KIR, LILRB and their Ligands' Genes as Potential Biomarkers in Recurrent Implantation Failure*. *Arch Immunol Ther Exp*, 10, 391-399.
- [29] Shreeve N., Depierreux D., Hawkes D. (2021) *The CD94/NKG2A inhibitory receptor educates uterine NK cells to optimize pregnancy outcomes in humans and mice*. *Immunity*, 6, 1231-1244.
- [30] GBA., FB., EPP. (1999) *Specific recognition of HLA-E, but not classical, HLA class I molecules by soluble CD94/NKG2A and NK cells*. *J Immunol*, 1, 305-313.
- [31] Wang Y. (2002) *Inhibitory receptor of CD94/NKG2A-C type lectin superfamily*. *Journal of Chinese Academy of Medical Sciences*, 6, 653-655.
- [32] Colucci F. (2022) *Uterine NK Cells Ace an "A" in Education: NKG2A Sets Up Crucial Functions at the Maternal-Fetal Interface*. *J Immunol*, 8, 1421-1425.
- [33] Xie M., Li Y., Meng YZ. (2022) *Uterine Natural Killer Cells: A Rising Star in Human Pregnancy Regulation*. *Front Immunol*, 13, 918550.
- [34] Jones AB., Rocco A., Lamb L S. *Regulation of NKG2D Stress Ligands and Its Relevance in Cancer Progression*. *Cancers (Basel)*, 14, 2339-2339.
- [35] Zhang J., Dunk CE., Kwan M. (2017) *Human dNK cell function is differentially regulated by extrinsic cellular engagement and intrinsic activating receptors in first and second trimester pregnancy*. *Cell Mol Immunol*, 14, 203-213.
- [36] Fan J., Shi J, Zhang Y. (2022) *NKG2D discriminates diverse ligands through selectively mechano-regulated ligand conformational changes*. *EMBO J*, 2, e107739-e107739.
- [37] Alves E., Mcleish E., Blancafort P. (2017) *Manipulating the NKG2D Receptor-Ligand Axis Using CRISPR: Novel Technologies for Improved Host Immunity*. *Front Immunol*, 12, 3263-3263.
- [38] Emanuele G., Marina C., Toshiyuki T. (2007) *Phosphatidylinositol 3-kinase activation is required to form the NKG2D immunological synapse*. *Mol Cell Biol*, 24, 8583-8599.
- [39] Mincheva-Nilsson. (2010) *Placental exosome-mediated immune protection of the fetus: feeling groovy in a cloud of exosomes*. *Expert Rev Obstet Gynecol*, 5, 619-634.
- [40] Burkova EE., Sedykh SE., Nevinsky GA. (2021) *Human Placenta Exosomes: Biogenesis, Isolation, Composition, and Prospects for Use in Diagnostics*. *Int J Mol Sci*, 22, 2158-2158.
- [41] Mei B., Zhang S., Chen Y. (2012) *Defects in NKG2D ligand expression result in failed tolerance induction at the maternal-fetal interface: A possible cause for recurrent miscarriage*. *Med Hypotheses*, 4, 465-467.
- [42] Sondes H., Nabil M., Safia M. (2014) *Polymorphisms in genes coding for the NK-cell receptor NKG2D and its ligand MICA in recurrent miscarriage*. *Am J Reprod Immunol*, 6, 577-585.