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Natural Killer (NK) Cell Receptors and their Role in Pregnancy and Abortion

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Abstract

Existing data suggest that decidual Natural Killer Cells (dNK CD3-CD56^{bright}CD16^{dim}/-) are important in early pregnancy (local response to pathogens, control of trophoblast invasion, uterine vascular remodeling), while in ongoing pregnancy they contribute to the acceptance of the embryo through various immunoregulatory mechanisms. In the so-called alloimmune abortions, CD3-CD56^{bright}CD16^{dim}/-NK cells are decreased in favor of CD3-CD56^{dim}CD16^{bright} NK cells, which are toxic for trophoblast. Most of the activating and inhibitory receptors regulating dNK function belong to the highly polymorphic KIR (Killer Immunoglobulin-like) family. KIRs have as ligands the only HLA molecules expressed on extravillous cytotrophoblast (HLA-C, -E, -G). The interactions of maternal KIR receptors with fetal HLA-C molecules provide an immunogenetic allorecognition system. If inhibitory KIRs recognize their specific ligands, they inhibit dNK activation for trophoblast damage. Otherwise, dNK are allowed to develop anti-trophoblast activity. Given the differences in both the KIR repertoire and the HLA-C allotypes among unrelated individuals, each pregnancy presents a different combination of maternal KIR receptors on dNK and self and non-self HLA-C allotypes on trophoblast. Current studies provide evidence for differences between the combinations arising in successful pregnancies to those found in cases of abortions.

Keywords: NK cells; NK receptors; KIR receptors; Pregnancy; RSA

Introduction

Natural Killer (NK) cells have been the focus of interest of immunologists for almost two decades. These large granular lymphocytes (LGL) are responsible for recognizing and killing transformed, stressed, and infected cells. They play a major role in innate immune responses, influence adaptive immune responses, and are involved in immunoregulation mechanisms. Initially, NK cells were considered as cells that kill target cells without prior sensitization or MHC (Major Histocompatibility Complex) restriction. Today, it has become clear that their function is determined by the expression of class I MHC, MHC-like or non-MHC molecules on targets, which are ligands of activating and inhibitory receptors that NKs express on their surface [1]. During their maturation process, NK cells are educated to recognize and tolerate "self" class I MHC molecules and react only against "foreign" (missing self-hypothesis). This "licensing" requires interaction of inhibitory NK receptors with "self" class I MHC molecules and makes NK cells efficient to recognize non-Ag-specific features ("altered self") through combinatorial signals from activating and inhibitory receptors [2,3].

NK Cell Phenotypes

NK cells consist 1-2% of lymphoid tissue found mainly in spleen. In the peripheral blood, they make up 5-15% of all lymphocytes and 70-95% of LGLs. They derive from stem cells, which differentiate to precursor NKs under the influence of growth factors and cytokines (IL-15, IL-2, IL-12). Going through various stages of maturation, they subsequently get the expression of a series of molecules with essential importance for their function (IL-2Rβ, CD2, CD7, CD8, CD16, CD56, CD57, CD45, CD94, KIRs) [2,4-6]. The most characteristic of these markers are the CD16 and CD56 molecules. CD16 (FcγRIII) is a low-affinity receptor, which binds to the Fc portion of Immunoglobulin G and activates the NK cell for antibody-dependent cell-mediated cytotoxicity (ADCC). CD56 is a neural cell adhesion molecule (NCAM), which mediates homotypic adhesion. Furthermore, the expression of NKp46, which is one of the Natural Cytotoxicity Receptors (NCR), appears to characterize NK cells in all species [1,7].

Based on the relative expression of CD16 and CD56, NK cells can be subdivided into different populations. The two major subsets are CD56^{dim}CD16^{bright} (low expression of CD56, high expression of CD16) and CD56^{bright} CD16^{dim}/−(high expression of CD56, low or no expression of CD16). CD56^{dim}CD16^{bright} cells, which represent at least 90% of all peripheral blood NKs, have cytotoxic function. Upon activation, they release perforin and granzymes from their granules, while they move to inflammation sites in response to chemokines released during inflammation by endothelial and innate immune cells [8]. CD56^{bright} CD16^{dim}/−cells constitute the majority of NK cells in secondary lymphoid tissues and are probably immediate precursors of the CD56 NKs. They are only weakly cytotoxic before activation, but upon the effect of cytokines (IL-12, IL-15 και IL-18) they immediately produce large amounts of interferon-γ (INF-γ) and may have immunoregulatory properties [9]. These cells constitute the major cell population of endometrial leukocytes (CD56 eGL: endometrial granulocytes), possibly after local differentiation [10].

NK Cell Receptors and Function

The function of NK cells is tightly regulated by a balance between activating and inhibitory signals transduced by corresponding various family receptors (NK cell Receptors–NKRs) that they express [11,12]. Depending on their structure, NKRs belong to the Immunoglobulin superfamily or to C-type lectins and are classified to at least five groups: Killer Immunoglobulin-like Receptors (KIR), Natural

Cytotoxicity Receptors (NCR), CD94/NKG2 receptors (Natural Killer Genes), NKG2D receptor, and LIR (Leukocyte Ig-like receptor)/ILT (Immunoglobulin–like transcripts) LIR receptors family (Table 1) [12,13].

All NKR families have both activating and inhibitory members. The contrasting function of the two types of receptors is due to structural differences of their molecules. The activating receptors bear to their trans membrane region amino acids, which associate to molecules containing immunoreceptor tyrosine-based activation motifs (ITAMs) and trigger NK cell cytotoxicity upon recognition of specific, widely distributed ligands (including MHC class I molecules) on target cells. However, the activation is controlled by the inhibitory receptors, which bear immunoreceptor tyrosine-based inhibition motifs (ITIMs), which upon engagement to specific MHC class I molecules on target cells activate the protein-tyrosine kinase SPH1 and deliver signals for inhibition of the NK action [14].

Family	Molecular structure	Receptors	Ligands
KIR (Killer Immunoglobulin-like Receptors)	Immunoglobulin Superfamily	KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DS1, KIR2DL4, KIR2DL1, KIR2DL2/3, KIR2DL5A, KIR2DL5B, KIR3DL1, KIR3DL2, KIR3DL3	HLA-A, Bw, -C, -G
NCR	Immunoglobulin Superfamily	NKp30, NKp44, NKp46, NKp80	Viral HA
ILT/LIR	Immunoglobulin Superfamily	LIR-1,2,3,4,5,6a,6b,7,8	HLA-G
CD94/NKG2	C-type lectins	NKG2A/B, NKG2C,NKG2F NKG2E, NKG2H	HLA -E
NKG2D	C-type lectins	NKG2D	MICA, MICB ULBPs

Table 1: NK cell Activating and Inhibitory Receptor Families.

A series of data on the molecular structure, the cellular expression patterns of NKRs, and the way they bind different regions of their MHC-I ligands and differentiate between tumor or virus-infected cells ("altered" targets") and normal cells, have helped in understanding the way of action and the biological role of NK cells. It is known that NK cells employ NKRs of all families for the recognition of different Human Leukocyte Antigens (HLA) class I molecules and the NKR repertoire has been shown to vary among different individuals [15]. Co-expression of multiple combinations of NKR with specificity for different HLA or non-MHC ligands on NK cells results in the regulation of the immune responses and in effectiveness of the anti-viral and anti-tumor defenses. The presence on all mature NK cells of at least one dominant inhibitory receptor (mainly KIR or CD94/NKG2) recognizing self HLA class I products prevents autoreactivity against normal host cells [12]. An individual may express receptors for which he does not possess the relevant HLA class I ligand but through these receptors he may encounter non-self HLA alleles during alloimmune reactions, such as the host versus graft and the graft versus host reactions in allogeneic transplantation, and the maternal immune response against the semiallogeneic fetus in pregnancy [16].

Today, a number of NKRs of each family are known and for most of them their ligands have been recognized. Most studied receptors are those of the KIR family, which have been found to play an important role at the feto-maternal interface.

KIR Receptors

KIR receptors are transmembrane glycoproteins expressed on NK cells and T lymphocytes. They possess characteristic Ig-like domains to their extracellular segment involved in the recognition of their ligands. Depending on the number of their Ig-like domains, KIR receptors are divided into two subgroups: the KIR2D (2 domains) and the KIR3D (3 domains). Activating KIRs have a short (S) cytoplasmic tail (2DS, 3DS), while inhibitory KIRs have a long (L) cytoplasmic tail with two ITIMs (2DL, 3DL) [17].

KIRs regulate the NK function by interacting with HLA class I molecules. Most of the KIR family members (2DL and 2DS) bind specifically to a subset of HLA-C allotypes possessing at position 80 of their molecule either asparagine (group C1 including the HLA-C*01, 03, 07, 08, C12 13, 14 and 1601/4 allotypes), or lysine (group C2 including the HLA-C*02, 04, 05, 06, 15, 1602, 17 and 18 allotypes) [18]. Other KIR members have been shown to recognize HLA-G (KIR2DL4) [19], HLA -A3/11 (KIR3DL2) or HLA-B molecules of the Bw4 serological group (KIR3DL1) [20]. Candidate ligands for some activating KIR members include non-MHC molecules, such as foreign or microbial antigens expressed on infected cells, normal cell surface proteins that are aberrantly expressed, stress-induced proteins or complexes of pathogen-derived peptides bound to MHC class I molecules [21].

The KIR gene locus maps to chromosome 19q.13.4 and has been shown to be polygenic and polymorphic [22]. The order of the KIR genes along the chromosome has been determined for two distinct haplotypes (A and B) differing in the number and the type of genes present (7-12 genes depending on the presence or absence of activating KIR genes). As a result of both allelic polymorphism at several KIR genes and variability in the number and type of genes present on any given haplotype, a great and continuously increasing number of different KIR profiles is identified among unrelated individuals. Obviously, there is only a small probability that two randomly selected individuals will have the same KIR genotype [15,23,24].

Studies have shown differences in the binding strength of the interactions of different KIRs with their ligands [25,26]. On the basis of these differences, Parham described a hierarchy for the strength of delivered inhibitory signals, suggesting that the KIR2DL1-C2 combination gives the strongest signal and the KIR2DL3-C1 combination the weakest one [26].

The high polymorphism that KIRs show at the level of genes, alleles, allotypes, expression and binding with their ligands, influences the NK cell action both in innate and adaptive immune responses. On the other hand, the receptor–ligand relationship between the products of two polymorphic loci as KIR and HLA, who work together in human immunity mediated by cytolytic lymphocytes, is likely to contribute to disease pathogenesis. Studies suggest that combination of specific MHC class I and KIR variants may be associated with susceptibility or resistance to infectious diseases (i.e KIR3DS1/Bw4-801 delays AIDS progression), autoimmune diseases (i.e KIR2DS1/2DS2; homozygous HLA-C susceptibility to psoriatic arthritis), cancer (KIR/2DL2/2DL3; HLA-C1 susceptibility to malignant melanoma), and pregnancy complications (i.e. AA KIR maternal haplotype and embryo HLA-C2

predisposition to preeclampsia) [27]. The association found with the outcome after mismatched haematopoietic stem-cell transplantation is of clinical importance: Absence in recipients of donor class I allelic groups known to be ligands for inhibitory KIRs has been shown to associate with leukemia relapse and graft rejection and also protect against graft-versus-host disease [28-30]. In response to these findings, clinical approaches have been suggested in order to manipulate receptor/ligand interactions for clinical benefit; searching for the appropriate HLA class I mismatch to set NK cells in action [31].

Finally, an emerging area of interest is the investigation of immunological/immunogenetic mechanisms in reproduction, where normal, as well as unsuccessful pregnancies, are seen with regard to decidual NK cell receptors and trophoblast expressed HLA molecules.

The Role of NK Cells in the Maintenance of Pregnancy

All knowledge on the biology of NK cells and their receptors, as well as data showing that HLA-C are expressed on extravillous subpopulations [32] and that more decidual NK cells than NK cells in the bloodstream express KIRs specific for HLA-C [33], led to the suggestion that the concept of "the fetus as an allograft" should encompass NK cells [34]. Incidentally, many studies have focused on decidual NK (dNK) cells and their function.

NK (CD3-CD56^{bright}CD16^{dim}) (usually called NK-like cells) are the dominant decidual cell population from the first stages of pregnancy through the first trimester. There is evidence that their proliferation and differentiation is synchronized with the secretor phase of the menstrual cycle, when estrogens and progesterone prepare the endometrium for a prospective pregnancy. During this phase, uterine stromal leukocytes increase highly (25% from 5%) as a result of NK cell influx from blood or other tissues or of reprogramming and differentiation of endometrial stromal cells to NK cells [35,36]. If pregnancy occurs, NK-like cells increase rapidly and are distributed broadly throughout decidua found in close proximity to extravillous trophoblast [37]. Due to their increased presence and direct contact with invading trophoblast, they have been considered important for the establishment of normal pregnancy. There is evidence that, simultaneously with blastocyst implantation and decidualization, uterine NK cells become activated, produce IFN-γ, perforin and other molecules, including angiogenetic factors, so that they may control trophoblast invasion through their cytotoxic activity and also initiate vessel instability and remodelling of decidual arteries to increase the blood supply to the feto-placental unit [38]. Furthermore, dNKs may be involved in cytokine-mediated immunoregulation of the maternal immune response producing Th2-type cytokines and growth factors, which result in placental augmentation and local immunosuppression and immunomodulation [39,40].

As in any other population of NK cells, the mode of action of dNKs involves a repertoire of activating and inhibitory receptors. Through their receptors, dNK cells may recognize selected epitopes on HLA-class I molecules expressed on invading trophoblast. It is interesting that the specific ligands for most of the receptors are the non-classical HLA class I molecules G and E as well as the classical HLA class I antigen C, which are the only HLA molecules expressed on extravillous trophoblast. Moreover, some of the receptors recognizing HLA-G and HLA-C epitopes are selectively expressed on dNK. The specific interaction of the NK cell receptors with trophoblastic antigens led to the concept of an embryo recognition model through an "NK cell allorecognition system". High affinity interactions of NK receptors with their ligands may provide self-signals to either a cytotoxic NK activation (Th1 response) or inhibition of activation and protection of trophoblast (Th2 response). Which one of the two responses will predominate depends on the action of the inhibitory receptors, which prevails over the action of the activating ones. So, if the inhibitory dNK receptors recognize their specific ligands on the trophoblast, they are expected to inhibit dNK activation for trophoblast damage, otherwise dNK are allowed to develop anti-trophoblast activity (Figure 1) [41].

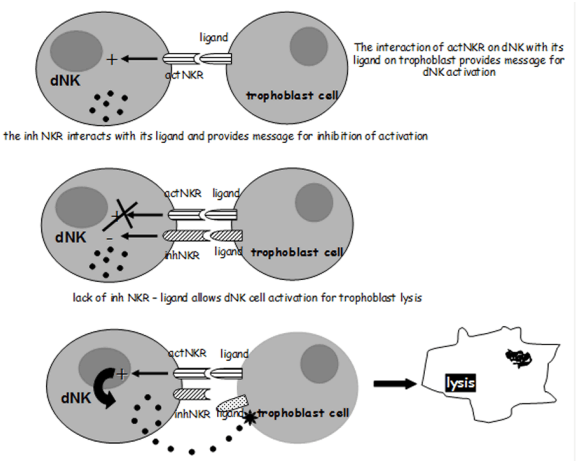

Figure 1: A model for the Interactions of NKRs on dNK cells with their ligands on trophoblast

Most studies that have investigated the effect of dNK receptors in the maintenance of pregnancy have specifically focused on the interactions involving HLA-G molecules because of their restricted distribution to placental tissues. HLA-G has been shown to be the ligand for at least three inhibitory receptors and the expression of some HLA-G isoforms has been shown to protect trophoblastic cells from lysis by activated cytotoxic cell clones [42]. Nevertheless, the control of the anti-trophoblast activity of dNK cells is probably the result of the cumulative interaction of several receptors on maternal dNK with different self and non-self-class-I molecules appearing on the HLA haplotypes expressed on trophoblast. Among the different NK receptors' interactions with their specific counterparts on trophoblast, the interactions between inhibitory receptors of the KIR family (inhKIR) and their ligands HLA-C molecules appear to be those mainly involved in the function of an NK cell-mediated allorecognition system in pregnancy [43]. Given the differences in both the inhKIR repertoire and the HLA-C allotypes among unrelated individuals, each pregnancy presents a different combination of maternal inhKIR receptors on dNK and self and non-self HLA-C allotypes on trophoblast. This combination is expected to ensure the appropriate receptor–ligand interactions to inhibit dNK anti-trophoblast activity, thus favoring pregnancy.

The Role of NK Cells in Abortion

Decidual NK cells are considered to be the main cell population involved in cases that the embryo is "rejected" by the mother (alloimmune abortions) [44,45]. Under the influence of Th1-type cytokines, they are stimulated to become classical NK cells expressing CD16 (CD3-CD16^{bright}CD56^{bright}), which can damage trophoblast

either directly by releasing cytolytic substances or indirectly by producing inflammatory cytokines [46].

An increase in NK cell numbers and /or activity in pre- or post-conceptional period in women with recurrent spontaneous abortions (RSA) or repeated implantation failures (RIF) are a significant clinical concern, while the immuno-phenotypic characteristics of NK cells in these women support the changes for their increased activity status [47]. Clinical studies have demonstrated that women who tend to abort have increased numbers of NK cells of the conventional CD3-$CD56^+CD16^+$ type in the uterus [48,49], as well as increased blood NK subsets and NK cell activity, all of which have been associated with abortion of chromosomally normal embryos [47,50,51]. A direct increase/activation and aborting effect of maternal NK cells may be infection-related. Thomas et al have suggested that subclinical herpes virus infection may be an important cause of peripheral blood NK cell stimulation in women with fertility problems and they associated antiviral treatment with a decrease of NK cell levels [52].

Considering the function of dNK cell receptors, the rejection of the embryo may be the result of a defect in the NK allorecognition system. Our studies in couples with RSA, as well as in cases of sporadic abortion have suggested that aborting women have a limited repertoire of inhKIR receptors or an imbalance of KIR receptors in favor of actKIRs [53,54]. Similar to the above data were provided by two collaborative studies performed in the frame of the 14th and 15th International Histocompatibility Workshops: A high percentage of women with RSA of alloimmune aetiology and women with RIF were found to have a divergence of the common AA KIR repertoire to a rather uncommon repertoire where A KIR haplotypes contain "extra" actKIRs [55]. Furthermore, many of the aborters were lacking the appropriate inhKIRs to interact with trophoblastic HLA-C molecules (lack of maternal inhKIR-fetal HLA-C epitope matching) or were found to possess inhKIRs that do not bind strongly their ligands (HLA-C) in order to sufficiently inhibit NK toxicity [56]. Although some authors appear not to agree with the above findings [57,58], other studies have also found the contribution of the predominance of an activating state in the balance between inhibitory and activating KIR receptors as well as in the KIR/HLA-C interactions to pregnancy loss [59-63]. Vargas et al have reported that women carrying a high content of activating KIR genes have about threefold increased probability to develop recurrent miscarriage [63]. In flow cytometric analyses for the expression of CD158a and CD158b inhibitory KIRs and CD161 activating KIR on peripheral NK cell subsets of RSA and RIF women, Yamada et al. and Ntrivalas et al. have reported an imbalance of inhibitory and activating receptor expression in favor of activating KIRs [64,65]. A higher activating potential resulting from particular maternal KIR/ fetal HLA-C combinations was shown in the study by Keramitzoglou et al. [66], which was performed on the abortion material and HLA-C ligands were directly genotyped on trophoblast cells. The individual combinations found in this study to associate with abortion as well as their comparison with findings from other relevant studies are shown on Table 2.

Findings in the study by Keramitzoglou et al.	Foreseen alloractivity	Result matching the hypothesis	*p*	Agreement with other studies
KIR2DL 1 ↓	Decreased inhibition	YES	0.007	Varla et al, Varla-Leftherioti et al. 2005 [53,54]
KIR2DS1 ↓	Decreased activation	NO	ns	Faridi et al. [61]
KIR2DL2 ↓	Decreased inhibition	YES	ns	Flores et al. [60]
KIR2DL3 ↓	Decreased inhibition	YES	ns	Flores et al. [60]
KIR2DL1-/ KIR2DS1+ ↓	Increased activation	YES	ns	Faridi et al. [61]
No of inhKIRs ↓	Decreased inhibition	YES	ns	Varla-Leftherioti et al. [54]
ABx Haplotypes ↓	Increased activation	YES	ns	Flores et al. [60]
KIR2DS1-C2 ↓	Increased activation	YES	ns	Varla-Leftherioti et al. [55]
No inhKIR/HLAC combination ↓	Increased activation	YES	0.038	Wang et al. [62]
KIR2DL1-C2 ↓	Decreased inhibition	YES	ns	Faridi et al. [61]
KIR2DL3-C1 ↓	Decreased inhibition	YES	ns	

Table 2: Comparison of KIR/HLA-C studies In RSA.

Conclusion

All the above data suggest that the toxic potential of decidual NK cells in cases of abortions is related to a decreased repertoire of women's' inhibitory KIRs and/or lack of epitope matching between maternal inhibitory KIR receptors and fetal HLA-C allotypes. Through the decreased inhibitory action of the KIR/HLA combinations, the activation of decidual NK cells is not blocked and these cells get the "license to kill", that is to damage the trophoblast and avert pregnancy.

Undoubtedly, the complexity of the NK allorecognition system is extremely high and makes the analysis of its impact in the outcome of pregnancy difficult: a) The alloreactive influence of the KIR/HLA-C leading players is the cumulative result of the interaction of different inhibitory and activating KIRs with "self" and "non self" trophoblastic molecules. b) The interactions are determined by two polymorphic immunogenetic systems. The analysis of HLA-C allotypes is rather easy by their grouping to C1 and C2, while KIR polymorphisms are projected with an enormous number of haplotypes differing in the number and the type of genes they contain. c) For the prediction of the alloreactivity one has to consider not only the molecules that are

involved but also the strength of the receptors-ligands binding, which is not possible to be estimated in all cases. d) Apart from HLA-C, decidual KIRs recognize several other ligands on trophoblast cells. e) It is possible that receptors of other NKR families (NKG2, ILT) get also involved interacting with their own (possibly polymorphic) ligands, many of which are not known. f) The signals delivered by the inhibitory or the activating KIRs are not always relatively enhancing or damaging. For instance, the activating receptors may enhance pregnancy through anti-viral activity. g) The appropriate or not interactions for the inhibition of NK cell anti-trophoblast effectiveness and embryo acceptance or not is a combination of receptors and lignads different in each couple and specific for each pregnancy.

The investigation of immunological/immunogenetic mechanisms in reproduction, where normal as well as unsuccessful pregnancies are seen with regard to decidual NK cell receptors and trophoblast expressed HLA molecules, remains a challenge. Increasing knowledge on KIR haplotypes and the structural basis of allelic specificity of KIR/HLA-C complexes is expected to help in better understanding of the suggested inhKIR/HLA-C allorecognition model in pregnancy. This will not only be of scientific interest but will also permit the application of similar analysis in couples with unexplained abortions and possibly give an immunogenetic aetiology of miscarriages in some cases. Perhaps, in the future, it may not be strange the KIR receptors to be used as therapeutic targets or (according to the example of donor selection in stem cell transplantation), KIR and KIR/HLA-C algorythms to be added to the tools of the assisted reproduction techniques for the selection of the appropriate gametes for successful pregnancy.

References

1. Caligiuri MA (2008) Human natural killer cells. Blood 112: 461-469.
2. Vivier E (2006) What is natural in natural killer cells? Immunol Lett 107: 1-7.
3. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S (2008) Functions of natural killer cells. Nat Immunol 9: 503-510.
4. Stites DP, Terr AI, Parslow TG (1994) Basic and clinical immunology. 8th edition, Appleton and Lange, Norwalk, Conn.
5. Colucci F, Caligiuri MA, Di Santo JP (2003) What does it take to make a natural killer? Nat Rev Immunol 3: 413-425.
6. Whiteside TL, Herberman RB (1994) Role of human natural killer cells in health and disease. Clin Diagn Lab Immunol 1: 125-133.
7. Cooper MA, Fehniger TA, Caligiuri MA (2001) The biology of human natural killer-cell subsets. Trends Immunol 22: 633-640.
8. Moretta A, Marcenaro E, Parolini S, Ferlazzo G, Moretta L (2008) NK cells at the interface between innate and adaptive immunity. Cell Death Differ 15: 226-233.
9. Poli A, Michel T, Thérésine M, Andrès E, Hentges F, et al. (2009) CD56bright natural killer (NK) cells: an important NK cell subset. Immunology 126: 458-465.
10. Hiby SE, King A, Sharkey AM, Loke YW (1997) Human uterine NK cells have a similar repertoire of killer inhibitory and activatory receptors to those found in blood, as demonstrated by RT-PCR and sequencing. Mol Immunol 34:419-430.
11. Yokoyama WM (1993) Recognition structures on natural killer cells. Curr Opin Immunol 1993;5:67-73. Lanier LL, NK cell receptors. Annu Rev Immunol 16:359-393.
12. Lanier LL (1998) NK cell receptors. Annu Rev Immunol 16: 359-393.
13. Lanier LL (2005) NK cell recognition. Annu Rev Immunol 23: 225-274.
14. Vivier E, Daëron M (1997) Immunoreceptor tyrosine-based inhibition motifs. Immunol Today 18: 286-291.
15. Uhrberg M, Valiante NM, Shum BP, Shilling HG, Lienert-Weidenbach K, et al. (1997) Human diversity in killer cell inhibitory receptor genes. Immunity 7: 753-763.
16. Gumperz JE, Valiante NM, Parham P, Lanier LL, Tyan D (1996) Heterogenous phenotypes of expression of the NKB1 natural killes cell class I receptor among individuals of different human histocomatibility antigens types appear genetically regulated, but not linked to major histocompatibility complex haplotype. J Exp Med 183:1817-1827.
17. Robinson J, Halliwell JA, McWilliam H, Lopez R, Marsh S (2013) IPD-the Immuno Polymorphism Database Nucleic Acids Research 41: D1234-1240.
18. Colonna M, Brooks EG, Falco M, Ferrara GB, Strominger JL (1993) Generation of allospecific natural killer cells by stimulation across a polymorphism of HLA-C. Science 260: 1121-1124.
19. Rajagopalan S, Long EO (1999) A human histocompatibility leukocyte antigen (HLA)-G-specific receptor expressed on all natural killer cells. J Exp Med 189: 1093-1100.
20. Cella M, Longo A, Ferrara GB, Strominger JL, Colonna M (1994) NK3-specific natural killer cells are selectively inhibited by Bw4-positive HLA alleles with isoleucine 80. J Exp Med 180:1235-1242.
21. Carrington M, Norman P (2003) The KIR Gene Cluster [Internet]. Bethesda (MD): National Center for Biotechnology Information (US).
22. Dupont B, Selvakumar A, Steffens U (1997) The killer cell inhibitory receptor genomic region on human chromosome 19q13.4. Tissue Antigens 49: 557-563.
23. Shilling HG, Guethlein LA, Cheng NW, Gardiner CM, Rodriguez R, et al. (2002) Allelic polymorphism synergizes with variable gene content to individualize human KIR genotype. J Immunol 168: 2307-2315.
24. Hsu K, Liu XR, Selvakumar A, Mickelson E, O'Reilly RJ, et al. (2002) Killer Ig-like receptor haplotype analysis by gene content: evidence for genomic diversity with a minimum of six basic framework haplotypes, each with multiple subsets. J Immunol 169: 5118-5129.
25. Bashirova AA, Martin MP, McVicar DW, Carrington M (2006) The killer immunoglobulin-like receptor gene cluster: tuning the genome for defense. Annu Rev Genomics Hum Genet 7: 277-300.
26. Parham P (2005) MHC class I molecules and KIRs in human history, health and survival. Nat Rev Immunol 5: 201-214.
27. Kulkarni S, Martin MP, Carrington M (2008) The Yin and Yang of HLA and KIR in human disease. Semin Immunol 20: 343-352.
28. Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, et al. (2002) Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 295: 2097-2100.
29. Velardi A, Ruggeri L, Mancusi A (2012) Killer-cell immunoglobulin-like receptors reactivity and outcome of stem cell transplant. Curr Opin Hematol 19: 319-323.
30. Mancusi A, Ruggeri L, Urbani E, Pierini A, Massei MS, et al. (2015) Haploidentical hematopoietic transplantation from KIR ligand-mismatched donors with activating KIRs reduces nonrelapse mortality. Blood 125: 3173-3182.
31. Velardi A, Ruggeri L, Alessandro, Moretta, Moretta L (2002) NK cells: a lesson from mismatched hematopoietic transplantation. Trends Immunol 23: 438-444.
32. King A, Burrows TD, Hiby SE, Bowen JM, Joseph S, et al. (2000) Surface expression of HLA-C antigen by human extravillous trophoblast. Placenta 21: 376-387.
33. Hiby SE, King A, Sharkey AM, Loke YW (1997) Human uterine NK cells have a similar repertoire of killer inhibitory and activatory receptors to those found in blood, as demonstrated by RT-PCR and sequencing. Mol Immunol 34: 419-430.
34. King A, Loke YW, Chaouat G (1997) NK cells and reproduction. Immunol Today 18: 64-66.
35. Gellersen B, Brosens IA, Brosens JJ (2007) Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives. Semin Reprod Med 25: 445-453.

36. Santoni A, Carlino C, Gismondi A (2008) Uterine NK cell development, migration and function. Reprod Biomed Online 16: 202-210.
37. King A (2000) Uterine leukocytes and decidualization. Hum Reprod Update 6: 28-36.
38. Ashkar AA, Di Santo JP, Croy BA (2000) Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. J Exp Med 192:259-270.
39. Clark DA, Arck PC, Jalali R, Merali FS, Manuel J, et al. (1996) Psycho-neuro-cytokine/endocrine pathways in immunoregulation during pregnancy. Am J Reprod Immunol 35: 330-337.
40. Chaouat G, Tranchot Diallo J, Volumenie JL, Menu E, Gras G, et al. (1997) Immune suppression and Th1/Th2 balance in pregnancy revisited: a (very) personal tribute to Tom Wegmann. Am J Reprod Immunol 37: 427-434.
41. Varla-Leftherioti M (2005) The significance of the women's repertoire of natural killer cell receptors in the maintenance of pregnancy. Chem Immunol Allergy 89: 84-95.
42. Menier C, Riteau B, Dausset J, Carosella ED, Rouas-Freiss N (2000) HLA-G truncated isoforms can substitute for HLA-G1 in fetal survival. Hum Immunol 61: 1118-1125.
43. Varla-Leftherioti M (2004) Role of a KIR/HLA-C allorecognition system in pregnancy. J Reprod Immunol 62: 19-27.
44. Labarrere CA (1989) Allogeneic recognition and rejection reactions in the placenta. Am J Reprod Immunol 21: 94-99.
45. Stern JJ, Coulam CB (1993) Current status of immunologic recurrent pregnancy loss. Curr Opin Obstet Gynecol 5: 252-259.
46. King A, Wheeler R, Carter NP, Francis DP, Loke YW (1992) The response of human decidual leukocytes to IL-2. Cell Immunol 141: 409-421.
47. Kwak-Kim J, Gilman-Sachs A (2008) Clinical implication of natural killer cells and reproduction. Am J Reprod Immunol 59: 388-400.
48. Vassiliadou N, Bulmer JN (1996) Immunohistochemical evidence for increased numbers of 'classic' CD57+ natural killer cells in the endometrium of women suffering spontaneous early pregnancy loss. Hum Reprod 11: 1569-1574.
49. Kwak JY, Beer AE, Kim SH, Mantouvalos HP (1999) Immunopathology of the implantation site utilizing monoclonal antibodies to natural killer cells in women with recurrent pregnancy losses. Am J Reprod Immunol 41: 91-98.
50. Coulam CB, Goodman C, Roussev RG, Thomason EJ, Beaman KD (1995) Systemic CD56+ cells can predict pregnancy outcome. Am J Reprod Immunol 33: 40-46.
51. Aoki K, Kajiura S, Matsumoto Y, Ogasawara M, Okada S, et al. (1995) Preconceptional natural-killer-cell activity as a predictor of miscarriage. Lancet 345: 1340-1342.
52. Thomas D, Michou V, Tegos V, Patargias T, Moustakarias T, et al. (2004) The effect of valacyclovir treatment on natural killer cells of infertile women. Am J Reprod Immunol 51: 248-255.
53. Varla-Leftherioti M, Spyropoulou-Vlachou M, Niokou D, Keramitsoglou T, Darlamitsou A, et al. (2003) Natural killer (NK) cell receptors' repertoire in couples with recurrent spontaneous abortions. Am J Reprod Immunol 49: 183-191.
54. Varla-Leftherioti M, Spyropoulou-Vlachou M, Keramitsoglou T, Papadimitropoulos M, Tsekoura C, et al. (2005) Lack of the appropriate natural killer cell inhibitory receptors in women with spontaneous abortion. Hum Immunol 66: 65-71.
55. Varla-Leftherioti M, Keramitsoglou T, Spyropoulou-Vlachou M, Papadimitropoulos M, Kontopoulou-Antonopoulou V, et al. (2007) 14th International HLA and Immunogenetics Workshop: report from the reproductive immunology component. Tissue Antigens 69 Suppl 1: 297-303.
56. Varla-Leftherioti M, Keramitsopoulou T, Parapanissiou E, Kurpisz M, Kontopoulou-Antonopoulou V, et al. (2010) HLA-DQA1*0505 sharing and killer immunoglobulin-like receptors in sub fertile couples: report from the 15th International Histocompatibility Workshop. Tissue Antigens 75: 668-672.
57. Hiby SE, Regan L, Lo W, Farrell L, Carrington M, et al. (2008) Association of maternal killer-cell immunoglobulin-like receptors and parental HLA-C genotypes with recurrent miscarriage. Hum Reprod 23: 972-976.
58. Witt CS, Goodridge J, Gerbase-Delima MG, Daher S, Christiansen FT (2004) Maternal KIR repertoire is not associated with recurrent spontaneous abortion. Hum Reprod 19: 2653-2657.
59. Faridi RM, Das V, Tripthi G, Talwar S, Parveen F, et al. (2009) Influence of activating and inhibitory killer immunoglobulin-like receptors on predisposition to recurrent miscarriages. Hum Reprod 24: 1758-1764.
60. Flores AC, Marcos CY, Paladino N, Arruvito L, Williams F, et al. (2007) KIR receptors and HLA-C in the maintenance of pregnancy. Tissue Antigens 69 Suppl1:112-113.
61. Faridi RM, Agrawal S (2011) Killer immunoglobulin-like receptors (KIRs) and HLA-C allorecognition patterns implicative of dominant activation of natural killer cells contribute to recurrent miscarriages. Human Reprod 26:491-497.
62. Wang S, Zhao YR, Jiao YL, Wang LC, Li JF, et al. (2007) Increased activating killer immunoglobulin-like receptor genes and decreased specific HLA-C alleles in couples with recurrent spontaneous abortion. Biochem Biophys Res Commun 360:696-701.
63. Vargas RG, Bompeixe EP, França PP, Marques de Moraes M, da Graça Bicalho M (2009) Activating killer cell immunoglobulin-like receptor genes' association with recurrent miscarriage. Am J Reprod Immunol 62: 34-43.
64. Ntrivalas EI, Bowser CR, Kwak-Kim J, Beaman KD, Gilman-Sachs A (2005) Expression of killer immunoglobulin-like receptors on peripheral blood NK cell subsets of women with recurrent spontaneous abortions or implantation failures. Am J Reprod Immunol 53: 215-221.
65. Yamada H, Shimada S, Morikawa M, Iwabuchi K, Kishi R, et al. (2005) Divergence of natural killer cell receptor and related molecule in the decidua from sporadic miscarriage with normal chromosome karyotype. Mol Hum Reprod 11: 451-457.
66. Keramitsoglou T, Dempegioti F, Dinou A, Spyropoulou-Vlachou M, LeBouteiller P, et al. (2011) Maternal KIR repertoire and KIR/HLA-C recognition model in early pregnancy and implantation failure. Adv Neuroim Biol 2: 99-103.