Tissue Antigens ISSN 0001-2815

KIR receptors and HLA-C in the maintenance of pregnancy

A. C. Flores[1], C. Y. Marcos[1], N. Paladino[1], L. Arruvito[1], F. Williams[2], D. Middleton[2, 3] & L. Fainboim[1]

1 Laboratorio de Inmunogenética, Hospital de Clínicas, Buenos Aires, Argentina
2 Northern Ireland Regional Histocompatibility and Immunogenetics Laboratory, Belfast City Hospital, Northern Ireland
3 University of Ulster, Coleraine, Northern Ireland

Key words
HLA; killer immunoglobulin-like receptors; natural killer cells; recurrent spontaneous abortions

Correspondence
Leonardo Fainboim
División Inmunogenética
Hospital de Clínicas 'José de San Martín'
Facultad de Medicina
Universidad de Buenos Aires
Av. Córdoba 2351 (1120)
Buenos Aires
Argentina
Tel: 54 11 5950 8756
Fax: 54 11 5950 8758
e-mail: lfainboim@hospitaldeclinicas.uba.ar

doi: 10.1111/j.1399-0039.2006.762_8.x

Abstract

The present study demonstrated that patients who have recurrent spontaneous abortions (RSA) presented a decreased number of killer immunoglobulin-like inhibitory receptors (KIR), in particular KIR2DL2. The KIR AA genotype was found increased in comparison with controls. Individuals AA will also be homozygous for 2DL3, which in contrast to 2DL2, show a weaker interaction with C1 ligands and therefore a weaker inhibition. The present study might support that in RSA patients, the balance between inhibitory and activating receptors present in natural killer cells is inclined toward an activating state that may contribute to pregnancy loss.

During the early phase of pregnancy, natural killer (NK) cells constitute the main lymphocytes in the human uterine decidua (1). These cells have been postulated as the protectors of the trophoblast by a mechanism so far not completely elucidated. NK cells possess a repertoire of activating and inhibitory receptors. The killer immunoglobulin-like receptors (KIRs) represent a highly polymorphic system not only by the number of alleles observed in the population but also for the variable number of genes expressed by different individuals. KIRs recognize as ligands on the trophoblast, human leukocyte antigen (HLA)-C, and HLA-G molecules (2).

To investigate whether there is an association between KIR receptors and the outcome of pregnancy we compared the KIR gene repertoire of a cohort of 30 fertile couples (without previous abortions) with a panel of 139 healthy controls and with 88 couples suffering from three or more recurrent spontaneous abortions (RSA).

Typing of KIR genes by PCR-sequence-specific oligonucleotide probing technique was performed as previously described (3). Two-sided Fisher's exact test for 2×2 tables was used to compare the KIR genes frequencies between the groups of patients and controls. Odds ratio (OR) with a 95% confidence interval was calculated to evaluate the relative risk in each patient's group. P values < 0.05 were considered statistically significant, P values < 0.01 very significant, and P values < 0.001 extremely significant.

On the basis of gene content, there are two distinct KIR haplotypes, termed A and B. The A haplotype has up to seven KIR loci with only one activating receptor, KIR2DS4. The B haplotypes show the presence of extra loci not present in the A haplotype. These include the inhibitory receptors KIR2DL2 and KIR2DL5 and the activating receptors KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DS1 (4).

The AA genotype was found present in 29.6% (26/88) of RSA patients *vs* 17.3% (24/139) of control women (a similar frequency of 17.1% was detected in fertile women); $P = 0.03$, OR = 2.0; Figure 1.

We found in RSA patients a decreased frequency of several inhibitory genes. However, only the decreased

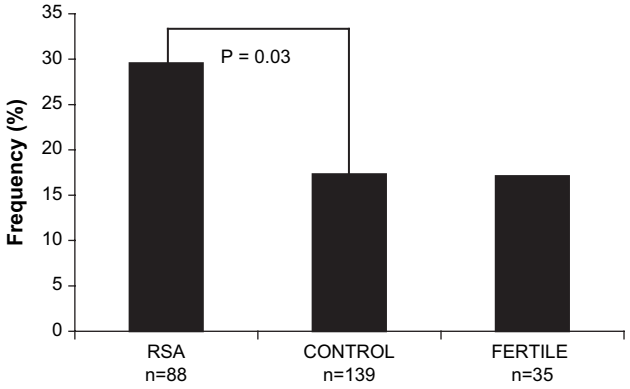

Figure 1 Percentage of women carrying AA genotype.

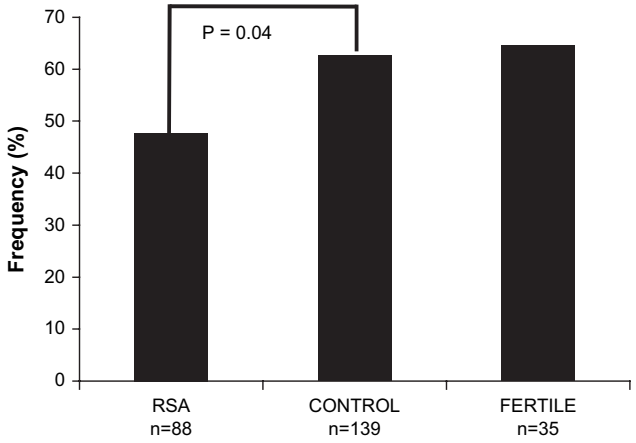

Figure 2 Phenotype frequency of killer immunoglobulin-like receptor 2DL2 in recurrent spontaneous abortions, fertile, and control women.

frequency of KIR2DL2 (receptor for HLA-C1) reached statistical significance ($P = 0.04$, OR = 0.5; Figure 2)

In summary, the present study demonstrated that RSA patients presented a decreased number of KIR inhibitory receptors in particular KIR2DL2. The latter is known to have a stronger inhibitory capacity than 2DL3 through its higher affinity to C1. Patients with preeclampsia also showed an increase of the AA genotype (5). Those patients were at a greatly increased risk of preeclampsia when the fetus possessed HLA-C belonging to the HLA-C2 group, which resulted from an increase of the inhibitory NK activity. In our study, it remains to be explained why the frequency of the AA genotype, with a predominance of inhibitory receptors, is increased in a subset of RSA patients. The NK activity results from a balance between inhibiting and activating receptors. In this context, 2DL1 which represents the highest inhibitory receptor is present in all AA individuals and the interaction 2DL1–HLA-C2 is the one which better contributes to a negative balance in NK signaling. However, AA individuals will also be homozygous for 2DL3, which in contrast to 2DL2, will show a weaker interaction with C1 ligands and therefore a weaker inhibition. Thus, the decreased frequency of 2DL2 present in RSA, might contribute to the overall balance between activation and inhibition that control NK activity toward an activating state that might contribute to the pregnancy loss.

Acknowledgments

This work was supported by grants from the Agencia Nacional de promoción Científica y Tecnológica, PICT 08814, and Welcome Trust Biomedical Research Collaboration Grant, GR072007MA.

Conflict of Interest Statement

All authors have declared no conflicts of interests.

References

1. King A, Burrows T, Loke YW. Human uterine natural killer cells. *Nat Immunol* 1996: **5**: 41–52.
2. King A, Burrows TD, Hiby SE et al. Surface expression of HLA-C antigen by human extravillous trophoblast. *Placenta* 2000: **21**: 376–87.
3. Middleton D, Williams F, Halfpenny I. KIR genes. *Transpl Immunol* 2005: **14**: 135–42.
4. Parham P. MHC class I molecules and KIRs in human history, health and survival. *Nat Rev Immunol* 2005: **5**: 201–14.
5. Hiby E, Walker J, O'Shaughnessy K et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med* 2004: **200**: 957–65.