



Killer cell immunoglobulin-like receptor gene associations with autoimmune and allergic diseases, recurrent spontaneous abortion, and neoplasms

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Killer cell immunoglobulin-like receptors (KIRs) are a family of cell surface inhibitory or activating receptors expressed on natural killer cells and some subpopulations of T lymphocytes. *KIR* genes are clustered in the 19q13.4 region and are characterized by both allelic (high numbers of variants) and haplotypic (different numbers of genes for inhibitory and activating receptors on individual chromosomes) polymorphism. This contributes to diverse susceptibility to diseases and other clinical situations. Associations of *KIR* genes, as well as of genes for their ligands, with selected diseases such as psoriasis vulgaris and atopic dermatitis, rheumatoid arthritis, recurrent spontaneous abortion, and non-small cell lung cancer are discussed in the context of NK and T cell functions.

Keywords: KIR genes, skin disease, rheumatoid arthritis, spontaneous abortion, cancer, viral diseases, viral infections

INTRODUCTION

Killer cell immunoglobulin-like receptors (KIRs) are a family of cell surface receptors. KIR proteins possess two (KIR2D) or three (KIR3D) immunoglobulin-like domains in their extracellular region. KIRs are expressed on natural killer (NK) cells and some subpopulations of T lymphocytes, and therefore may influence the activation of both cell types. They do it either by inhibition of cell activation [inhibitory KIRs, with long (L) cytoplasmic tail – KIR2DL and KIR3DL – which contains immunoreceptor tyrosine-based inhibitory motifs, ITIMs], or by activation of a cell [activating KIRs, KIR2DS, and KIR3DS, with short (S) cytoplasmic tail having no signaling motifs but associated with adapter molecule, DAP12 homodimer, which possesses immunoreceptor tyrosine-based activating motifs, ITAMs]. Upon ligand binding by inhibitory KIR, tyrosine residues in its ITIMs become phosphorylated, which is recognized by a phosphatase, which then dephosphorylates proteins of the signaling pathway, phosphorylated previously due to cell activation. On the other hand, ligand binding by activating KIR results in tyrosine phosphorylation in ITAMs of DAP12 molecule, and this leads to activation of kinases of signaling pathway and cell activation. KIR ligands, where known, are HLA class I molecules (Table 1). All allomorphs of HLA-C are recognized by some inhibitory KIRs, whereas less than 50% of HLA-A and HLA-B allomorphs present in human populations are recognized by KIRs (Parham et al., 2012a). Differing in the amino acid residue in position 80, HLA-C allomorphs fall into two groups, C1 (Asn80) and C2 (Lys80), recognized by KIR2DL2/KIR2DL3 and KIR2DL1/KIR2DS1, respectively (Table 1). As a rule, when inhibitory and activating KIRs have the same or similar HLA

specificity (such as KIR2DL1 and KIR2DS1), then binding of inhibitory KIR to its ligand is characterized by higher affinity than binding of activating KIR to the same ligand (Vales-Gomez et al., 1998). This protects normal cells of the body, displaying normal quantity of HLA class I molecules, against the NK cell attack (efficient inhibition), but ensures killing of virus-infected or malignant cells with low or none expression of one or all HLA class I alleles (non-efficient inhibition; “missing-self” theory, Ljunggren and Kärre, 1990).

KIR genes are clustered in the leukocyte receptor complex (LRC) of genes located in the 19q13.4 region and are characterized by both allelic (high numbers of variants) and haplotypic (different numbers of genes for inhibitory and activating receptors on individual chromosomes) polymorphism (Parham et al., 2012a). Some *KIR* genes (*KIR3DL2*, *KIR3DL3*, and *KIR2DL4*) are called “framework genes,” because they are present in all haplotypes. Other genes are present only in some of them, in multiple different combinations. Haplotypes consisting mostly of inhibitory genes (so called “A” haplotypes) tend to be associated with lower risk of autoimmune diseases, but higher risk of viral infections than haplotypes (“B” haplotypes) containing several activating *KIR* genes (see Parham, 2005; Khakoo and Carrington, 2006; Kusnierczyk, 2006; Boyton and Altmann, 2007; Campbell and Purdy, 2011)¹.

Associations of *KIR* and their *HLA* ligand genes have been studied in multiple human diseases, and reviewing all of these here would not be possible. Therefore, selected clinical conditions,

¹<http://www.allelefreqencies.net/diseases/dis6001a.asp>

Table 1 | Ligands of KIR molecules (based on Kusnierczyk, 2006; Graef et al., 2009; Campbell and Purdy, 2011; Parham et al., 2012b; and references therein, modified).

KIR	Ligand
2DL1	C2
2DL2	C1 and some C2
2DL3	C1
2DL4	HLA-G1
2DL5	Unknown
2DS1	C2
2DS2	Unknown
2DS3	Unknown
2DS4	HLA-A*11, some C1 (*1601 > *0102,1402), C2 (*0502 > 0202 > 0401), and non-identified melanoma antigen
2DS5	Unknown
3DL1	HLA-Bw4
3DL2	HLA-A*03, A*11, and microbial CpG DNA
3DL3	Unknown
3DS1	Unknown (HLA-Bw4?)

HLA-C allele groups (i.e., KIR2D ligands):

C1 (*Asn80*) – C*01,03,07,08,12,13,1402,1507,1601; HLA-B46.

C2 (*Lys80*) – C*02,04,05,06,0707,12042,1401,15(without 1507),1602,17.

most familiar to my laboratory, are summarized and discussed below.

SKIN DISEASES: PSORIASIS AND ATOPIC DERMATITIS

PSORIASIS

Psoriasis is a multifactorial skin disease with autoimmune features, which are manifested by T lymphocyte infiltration to both dermis and epidermis (Lew et al., 2004) and by antipsoriatic activity of immunosuppressants such as recombinant soluble CTLA-4 (Sivamani et al., 2012). Although etiology of this disorder is still not definitely elucidated, it is known that both environmental and genetic factors are involved. Genome-wide association studies revealed at least 13 psoriasis susceptibility loci (*PSORS1-13*)². Among these, the strongest linkage and association was reproducibly described for *HLA-Cw*06* allele located on *PSORS1* locus and encoding a ligand for KIR2DL1 and KIR2DS1 receptors (see text footnote 2). Several lines of evidence show contribution of NK or T lymphocytes expressing NK cell receptors, among them KIRs (Gilhar et al., 2002; Liao et al., 2006). Therefore, we examined whether inhibitory or activating *KIR* genes might be associated with susceptibility to psoriasis vulgaris, most common clinical form of this disease. We typed 114 and 116 patients for *HLA-C* alleles and *KIR* genes, respectively, and compared their frequencies with those in 123 unrelated healthy control individuals. We found, first, a strong association of psoriasis with *HLA-Cw*06*, which was strongest in individuals whose age at disease onset was up to 20 years, and decreased in patient groups with later age at onset (Luszczek et al., 2002). Not surprisingly, we found an association of

KIR2DS1 gene, coding for an activating receptor recognizing *HLA-Cw*06* (*HLA-Cw*06* belongs to C2 group of *HLA-C* epitopes), with psoriasis vulgaris. However, in contrast to *HLA-Cw*06*, association of *KIR2DS1* with psoriasis seemed stronger in higher age at onset values, although the age effect was not significant because of small numbers of patients with late disease onset (Luszczek et al., 2004). Very similar association of *KIR2DS1* (and *KIR2DL5* in addition, which was not analyzed in our study) was simultaneously published for Japanese population, genetically distant from Poles (Suzuki et al., 2004), and confirmed later in Swedish and Brazilian Caucasians with psoriasis vulgaris (Holm et al., 2005; Jobim et al., 2008), but not in Swedes with guttate psoriasis (Holm et al., 2005) or in Taiwanese Chinese with plaque psoriasis (Chang et al., 2006; see Table 2). Interestingly, *KIR2DS1* gene appeared associated also with psoriatic arthritis (Martin et al., 2002b; Holm et al., 2005; Williams et al., 2005; Table 2). In this latter disease, both *KIR2DS1* in the absence of C2, and *KIR2DS2* in the absence of C1 group *HLA-C* alleles were observed associated with psoriatic arthritis (Martin et al., 2002b; Nelson et al., 2004) in addition to other genes (*HLA-B*27* and *HLA-Cw*0602*), although in American population the effect of *KIR2DS1* was independent from C2 presence (Williams et al., 2005).

We observed also some effects of other *KIR* genes in psoriatic patients positive for *KIR2DS1*: namely, increased frequency of a deletion variant of *KIR2DS4* and decreased frequency of *KIR2DS3* and *KIR2DS5* gene in comparison to *KIR2DS1*-positive controls (Ploski et al., 2006). A seemingly protective effect of *KIR2DS5* gene presence was seen also in other diseases (Nowak et al., 2010). The deletion variant of *KIR2DS4* gene (Hsu et al., 2002a,b; Maxwell et al., 2002, 2004) potentially encodes a soluble protein, although this has not been proven, and its transcription level is very low (McErlean et al., 2010).

In summary, *KIR2DS1* gene seems to be a major factor in the LRC region contributing to the susceptibility to psoriasis vulgaris and related diseases which are also associated with a gene for its ligand, *HLA-Cw*06*.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic or relapsing inflammatory skin disorder of complex etiology, affecting up to 20% of children and often followed later by development of asthma and other allergic diseases. Multiple immunological disturbances were described. Disruption of epidermal barrier increases a susceptibility of AD patients to microbial infections, both bacterial (*Staphylococcus aureus* in most cases) and viral (localized or disseminated infections, most often by *Herpes simplex* virus; De Benedetto et al., 2009; Boguniewicz and Leung, 2011). As NK cells are among many cell types whose activity might be biased in AD, we were interested whether *KIR* and *KIR* ligand genotype of AD patients would differ from that of healthy persons. We compared *KIR* gene frequencies in a group of 240 patients diagnosed with AD with those in 690 healthy individuals representative for several regions of Poland. Distribution of *KIR* genes in both groups was very similar, with one exception: *KIR2DS1* gene was present less frequently in patients than in controls. This latter observation was confirmed on the second cohort of 201 patients from a different region of Poland (Niepieklo-Miniewska et al., submitted).

²<http://omim.org/entry/177900>

Table 2 | KIR2DS1 gene associations with clinical forms of psoriasis in different ethnic groups.

Diagnosis	Ethnicity	Number of patients	Number of controls	KIR2DS1 association	Odds ratio ^a	P	Reference
PV	Polish	116	123	Yes	5.55	<0.0001	Luszczek et al. (2004)
PV	Swedish	240	372	Yes	1.48	0.0234	Holm et al. (2005)
PV	Braz. Cauc.	79	110	Yes	2.43	0.005	Jobim et al. (2008)
PV	Japanese	96	50	Yes	2.09	<0.05	Suzuki et al. (2004)
PP	Chinese	178	203	No	NA	NS	Chang et al. (2006)
PG	Swedish	80	372	No	NA	NS	Holm et al. (2005)
PA	Swedish	75	372	Yes	1.65	0.0555	Holm et al. (2005)
PA	Canadian	366	299	Yes	1.60	0.004	Martin et al. (2002b)
PA	Am. Cauc.	75	90	Yes	2.41	0.0046	Williams et al. (2005)

^aIf not given in a publication, then calculated on the basis of its data.

Abbreviations: PV, psoriasis vulgaris; PP, plaque psoriasis; PG, guttate psoriasis; PA, psoriatic arthritis; NA, not applicable; NS, non-significant.

The reason why *KIR2DS1* gene has been found associated with psoriasis and psoriatic arthritis (see Psoriasis) but seemingly protective against another inflammatory skin disease, AD, is not clear. Psoriasis is believed to be a Th1-regulated disease, whereas Th2 response dominates in AD (Rabin and Levinson, 2008; von Bubnoff et al., 2010). This division is not so sharp in nature, however (Guttman-Yasky et al., 2011), although microarray analysis confirms it to a great extent (Nomura et al., 2003; Choy et al., 2012). Keratinocytes hyperproliferate in psoriasis but undergo apoptosis in AD (Albanesi et al., 2007; Kastelan et al., 2009; Rebane et al., 2012). Therefore, different *KIR2DS1*-positive cell subpopulations may contribute to both types of the disease, resulting in opposite associations of *KIR2DS1* gene.

RHEUMATOID ARTHRITIS

Another disease, where *KIR* gene associations were examined, was rheumatoid arthritis (RA). This disorder is a chronic systemic inflammatory polyarthritis affecting about 1% of individuals in Caucasian populations, and T cells contribute to its pathomechanism (Jacob and Jacob, 2012). The involvement of NK cells in RA was also described (Dalbeth et al., 2004; Falgarone et al., 2005). RA is a multifactorial disease, and strongest genetic association was reproducibly shown for so called shared epitope of HLA-DR; however, it explains only one-third to a half of the genetically determined susceptibility to the disease (Bowes and Barton, 2008). The expression of *KIR2DS2* molecule on T cells with unusual phenotype, CD4⁺CD28⁻KIR⁺, and an association of *KIR2DS2* but not *KIR2DS1* gene with vascular inflammatory complication of RA were described by Joerg Goronzy's group (Yen et al., 2001). Other *KIR* genes were not tested by these authors. Therefore, we compared *KIR* gene frequencies in 177 RA patients and 243 control individuals. Although no differences between the whole group of patients and controls were found (Majorczyk et al., 2007) – similarly to simultaneously published study of Northern Irish RA patients (Middleton et al., 2007), nevertheless *KIR2DS2* gene was associated with vasculitis also in our population of patients. In addition, frequency of *KIR2DL2* gene, not tested by Yen et al. (2001), was also increased in vasculitis (Majorczyk et al., 2007). Both these genes are in very strong linkage disequilibrium in Caucasians, which makes differentiation

between their effects impossible. However, increased frequency of CD4⁺CD28⁻ T cell clones positive for *KIR2DS2* but negative for *KIR2DL2* gene expression, observed in RA vasculitis by Yen et al. (2001), speaks for the role of the former gene in this complication of RA. Interestingly, CD4⁺CD28⁻ T cells described in RA vasculitis were found only in human cytomegalovirus-seropositive, but not in HCMV-negative RA patients, and their specificity was predominantly directed toward HCMV antigens. If they cross-react weakly with some autoantigens, then *KIR2DS2* binding to yet unknown ligands might boost these T cells to autoaggression (van Bergen and Koning, 2010).

Furthermore, the frequencies of *KIR2DS1* and *KIR3DS1* were lower in our patients without bone erosions than in those with erosions and controls. Another interesting finding we made was that RA patients positive for *KIR2DL3* and negative for *KIR2DS3* had earlier disease diagnosis. On the other hand, we observed no associations of *KIR* genes with autoantibodies: rheumatoid factor or anti-cyclic citrullinated peptide (Majorczyk et al., 2007).

Thus, although a susceptibility to RA does not seem to be influenced by particular *KIR* genes, some clinical manifestations of this disease such as vasculitis, bone erosions, and age at onset, are associated with distinct *KIR* genes, which might reflect participation of different subpopulations of T and/or NK cells.

IMMUNOGENETICS OF REPRODUCTION

RECURRENT SPONTANEOUS ABORTION

Spontaneous abortion is the most frequent disorder of human pregnancy. Approximately 10–15% of pregnancies end in miscarriage during the first trimester, and even many more spontaneous abortions go undetected. Although most are sporadic and non-recurrent, there is a subset comprising about 1% of all pregnancies which end with recurrent spontaneous abortion (RSA). This is defined as at least three consecutive miscarriages before 20 weeks of gestation (Matthiesen et al., 2012). RSA may have a number of causes (Harris, 2010; Beaman et al., 2012; Matthiesen et al., 2012), as molecular regulation of placentation is very complex, involving both promoting and inhibitory factors secreted by several cell types: decidual stromal cells, decidual macrophages, and decidual NK (dNK) cells (Knoefler and Pollheimer, 2012). Therefore, some of the cases may result from insufficient activity of dNK cells

(Harris, 2010; Parham and Guethlein, 2010). NK cells constitute a large leukocyte population in the endometrium and they come in close contact with allogeneic extravillous trophoblast (EVT) cells in early pregnancy decidua, which is necessary for the placentation. EVT cells, in contrast to villous trophoblast cells, do express both maternal and paternal HLA-C molecules (Hiby et al., 2010). Moreover, HLA-C molecules on trophoblast cells form stable heterotrimeric heavy chain/ β 2-microglobulin/peptide complexes in contrast to decidual and other cells which express not only these heterotrimers, but also free HLA-C heavy chains (Apps et al., 2008). In addition, dNK cells are biased toward expression of HLA-C-binding KIRs (Male et al., 2011). Therefore, their polymorphic KIRs recognizing polymorphic HLA-C molecules inherited from the father by semiallogeneic fetus may play an important role in the outcome of pregnancy. Indeed, recent studies suggest that, in addition to their role in the innate immune response to infection and cancer, KIR-HLA (and particularly KIR-C1/C2) interactions control a proper formation of placenta (Chazara et al., 2011; Colucci et al., 2011; Parham et al., 2012b). Several investigators reported some associations of KIR genes with RSA.

First, Varla-Leftherioti et al. (2003) reported a comparison of 26 Greek couples with RSA and 26 fertile couples. They observed twice lower percentage of genotypes containing genes for all three HLA-C binding KIR2DL receptors in RSA couples as compared to control ones, and six times higher fraction of women not possessing KIR2DL genes present in their husbands (Varla-Leftherioti et al., 2003). These findings were confirmed on further 15 spontaneously aborting women compared with 15 women undergoing elective abortion from the Greek population; in addition, in 33.3% of spontaneously aborting women, fetal tissue did not possess a ligand for the inhibitory KIR(s) of the mother (Varla-Leftherioti et al., 2005). However, both these studies were performed on low numbers of patients and controls, and their results were not confirmed by the same authors on larger cohorts involving different ethnic groups (Varla-Leftherioti et al., 2007, 2010). Simultaneously, another group of investigators published a series of thorough studies on the English population, showing that: (a) KIR AA genotype frequency was significantly increased, and frequencies of B haplotype-associated KIR genes were decreased in 95 RSA cases compared to 269 controls (Hiby et al., 2008); (b) frequency of C2 group HLA-C alleles was significantly increased in male partners of RSA women, whereas these women exhibited an increased frequency of KIR AA genotype (which contains C2-specific KIR2DL1 gene; Hiby et al., 2008); and (c) KIR AA frequency was increased in affected mothers (i.e., combined mothers with preeclampsia, RSA, and restricted fetal growth) only when the fetus possessed more C2 genes than the mother, i.e., C2/C2 fetus in C1/C2 mother and C1/C2 fetus in C1/C1 mother (Hiby et al., 2010). This study showed also that the protective effect of haplotype B genes is located in telomeric part of the KIR region (TelB, containing KIR2DS1 gene), whereas no single gene from the haplotype A was found associated with RSA (Hiby et al., 2010). This latter result is not contradicting the association of AA genotype with RSA in England mentioned above, because all of A haplotype genes may appear also in some B haplotypes (Parham, 2005): both a centromeric (CenA) or telomeric (TelA) haplotype A segment may be linked to telomeric (TelB) or centromeric (CenB) segment from a B haplotype, respectively (Cooley et al., 2010; Parham and

Guethlein, 2010; Pyo et al., 2010; Chazara et al., 2011), and only CenA/CenA-TelA/TelA genotypes were named "AA" in the past, all other ones being "BB" or "Bx."

There were also reports on KIRs and HLA-C in RSA in other populations. Hong et al. (2008) described an association of KIR2DL2 (a B haplotype gene), but not any other KIR gene with RSA in Chinese (Hong et al., 2008). However, this study was made on extremely low number of patients ($N = 16$) and low number of controls ($N = 41$), and the result was not corrected for the number of comparisons. Indeed, another Chinese study on higher numbers of individuals (73 RSA couples and 68 control couples) did not confirm KIR2DL2 increase, but has rather shown an increase of activating KIR genes, 2DS1 and 2DS5 and association of RSA with higher numbers of activating KIRs (Wang et al., 2007). Similarly, in 68 Brazilian Caucasian RSA patients, genotypes with five or six activating KIR genes were significantly more frequent than in 68 controls (Vargas et al., 2009), although no single KIR gene reached significance in frequency distribution in this (Vargas et al., 2009) and other (Witt et al., 2004) study on Brazilian women. In northern India, two KIR A haplotype genes, 2DL1 and 2DS4, were found less frequently in 177 RSA patients than in 200 ethnically matched controls; a combination of KIR2DL1 in the mother with C2/C2 genotype in both parents was also less frequent in patients, whereas KIR2DL1 in the mother with C1/C1 genotype in both parents was more frequent in RSA couples than in controls. There were also some combinations of B haplotype-associated genes KIR2DS1 and KIR2DS2 with C1 and C2 genotypes which were differently distributed among RSA couples and controls (Faridi and Agrawal, 2011).

We typed 85 Polish Caucasian women with RSA and 117 healthy control women with at least two healthy born children for KIR genes and HLA-C C1 and C2 markers. We also tested their partners for HLA-C alleles and for C1 and C2. Similarly to some other investigators, we did not observe any differences in frequencies of individual KIR genes between RSA and control women (Nowak et al., 2011b). However, we found that genotypes with low activating to inhibitory KIR ratios were overrepresented in our RSA sample, whereas equilibrium between these two gene kinds seemed to favor a success of pregnancy (Nowak et al., 2009). Nevertheless, AA (most inhibitory) genotype was non-significantly less frequent in RSA than in control (Nowak et al., 2011b), and this result was confirmed by a significant decrease of this genotype in Turkish RSA patients (Ozturk et al., 2012). This result does not, again, seem to contradict the association of low activating to inhibitory KIR ratios with RSA mentioned above, because some inhibitory KIR genes (KIR2DL5A, KIR2DL5B) appear only in B haplotypes and therefore contribute to lower activating to inhibitory gene ratio, and some inhibitory KIR genes associated with A haplotype appear also in some B haplotypes, decreasing activating to inhibitory KIR ratio.

Furthermore, in our study women with AA KIR and C1C2 HLA-C genotype pregnant with C2C2 males were present in control but completely absent from the RSA group, whereas C1C1 and C2C2 AA women with C2C2 partners were absent from control but present in RSA (Nowak et al., 2011b). Our results are somewhat different from these of Hiby et al. (2010), where C1C2 AA women bearing C2C2 fetus were more frequent in affected pregnancies (RSA included) than in control, whereas we observed C1C2 AA women pregnant with C2C2 males only in control but

not in RSA (Nowak et al., 2011b). Also, C1C1 AA women with C1C2 fetus were more frequent in affected group of Hiby et al. (2010), but C1C1 AA mothers with C1C2 father were more frequent in control than in RSA in our sample (Nowak et al., 2011b). These results can not be directly compared, however, as we had no possibility to *HLA-C*-type fetal tissue, particularly in our control, because elective termination of normal pregnancy is legally forbidden in Poland except for some criminal cases and endangered mother's life. Therefore, in our case, we could predict fetal *HLA-C* genotype and its parental origin only for some couples (e.g., C1C1 mother and C2C2 father and vice versa).

In summary, results of studies published so far frequently bring conflicting results. The reasons for these discrepancies may be multiple. Some studied populations were genetically very distant, with different *KIR* and *HLA-C* genotype frequencies. This is exemplified by opposite results with *KIR2DS1* association with RSA, negative in England (Hiby et al., 2008, 2010) but positive in China (Wang et al., 2007). In most studies the numbers of patients and controls were low, and extremely low in some reports, as shown in **Table 3**. Some associations detected in small population samples were not confirmed in larger cohorts. Also, criteria for inclusion of patients and controls were not the same, as we discussed elsewhere (Nowak et al., 2011b). Therefore, there seems to be a need for standardization of studies on genetics of RSA and other pregnancy disorders in different ethnic groups.

AN INTACT *KIR2DL4* GENE DOES NOT SEEM NECESSARY FOR FEMALE FERTILITY

KIR2DL4 differs from other *KIR* genes: (i) it has long cytoplasmic tail which, however, contains only one ITIM sequence; (ii) it has a positively charged arginine residue in the transmembrane region which gives it a possibility to make a complex with the $Fc\epsilon R1\gamma$ chain containing an ITAM sequence; (iii) it is not clonally distributed like other KIRs but expressed in all NK cells; (iv) on resting NK cells, it is expressed mostly not at the cell surface but in early endosomes where it can bind a soluble *HLA-G* molecule (its only known ligand), which is present (in physiological conditions) only on trophoblast cells invading decidua during early pregnancy; and it transmits an activating rather than inhibitory signal inducing cytokine secretion but not cytotoxicity (see a recent review by Rajagopalan and Long, 2012, and references therein).

KIR2DL4 is one of so called framework genes, present in all *KIR* haplotypes, similarly to *KIR3DL2*, *KIR3DL3*, and *KIR3DP1* (Parham et al., 2012a). Therefore, interaction of *KIR2DL4* expressed in dNK cells with *HLA-G* expressed by trophoblast was suspected to be very important for normal pregnancy (Carosella et al., 2001; Ober et al., 2003; Yan et al., 2007). However, healthy born individuals with defects of *HLA-G* gene were detected (Ober et al., 2003). Nevertheless, they were able to produce truncated form of *HLA-G* molecules which could substitute for the normal *HLA-G* (Hunt and Langat, 2009). Although *KIR2DL4* gene was believed to be present in all people worldwide, several individuals lacking this gene were found in different populations in recent years. First one was an African immigrant from Bubi tribe (Bioko island, Equatorial Guinea), a woman who delivered five healthy children and experienced only one spontaneous abortion (Gomez-Lozano et al., 2003). Then, several single cases from Pakistan,

Trinidad (also Pakistani by origin), South Turkey, and Solomon Islands were reported to the allele frequency database (Gonzalez-Galarza et al., 2011)³. We have also found, in the Polish population of 690 healthy individuals, one woman lacking *KIR2DL4* gene (Nowak et al., 2011a). As her DNA was taken from paternity testing, she must have delivered at least one baby, and therefore was fertile. Interestingly, she had a *KIR* genotype identical to that of the Bubi woman mentioned above: *3DL3-2DS2-2DL2-2DL5B-(del)-2DS5-2DS1-3DL2*. Unfortunately, her personal and family data must have remained anonymous, as required by the Bioethical Committee for samples from paternity testing, therefore neither studies on her family were possible nor data on her further reproductive success were available (Nowak et al., 2011a). However, her case, and particularly that of Bubi individual, indicate that the presence of *KIR2DL4* gene is not absolutely necessary for successful human reproduction, similarly to the presence of intact *HLA-G* gene.

NEOPLASTIC DISEASES

Both NK cell cytotoxic activity (Herberman et al., 1975a,b; Kiessling et al., 1975a,b) and "missing-self" phenomenon (Ljunggren and Kärre, 1990) were discovered in experimental mouse models using tumor cells as targets for NK activity. Transformed neoplastic cells are believed to escape from elimination by cytotoxic T cells due to a reduction or loss of some or all *HLA* class I (*HLA-I*) molecules, which in turn exposes them to the attack from NK cells (Ljunggren and Kärre, 1990; Bubenik, 2004; Parham, 2005; Khakoo and Carrington, 2006; Purdy and Campbell, 2009). It has been shown that NK cells may lyse not only cells of established human tumor cell lines but also freshly isolated human tumor cells (Carlsten et al., 2009). Since *KIR* phenotype affects activity of NK cells (and subpopulations of T lymphocytes), one can expect that a prevalence of neoplasms may be influenced by it. Therefore, many investigators examined distribution of *KIR* genes and their ligands as well as their expression in several tumor systems, experimental and clinical (Parham, 2005; Khakoo and Carrington, 2006; van der Meer et al., 2008). We looked whether prevalence of non-small cell lung cancer (NSCLC) might be associated with genes for KIRs and their ligands in the Polish population.

NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer constitutes 85% of lung cancer cases which are a major cause of cancer mortality worldwide. It is a multifactorial disease with a strong environmental (mostly cigarette smoking) influence, but genetic factors also play a role⁴. In NSCLC, NK cells infiltrate rather peritumoral than tumor tissue, in contrast to T lymphocytes (Esendagli et al., 2008; Schneider et al., 2011), and these NK cells which do infiltrate the tumor are predominantly CD56^{bright}, negative for NK cell receptors (including KIRs), and exhibit low cytotoxic activity *ex vivo* (Carrega et al., 2008; Esendagli et al., 2008). On the other hand, a tumor-specific cytotoxic T cell clone isolated from tumor infiltrating lymphocytes in an NSCLC patient expressed *KIR3DL2* but not other KIRs,

³<http://www.allelefreqencies.net/>

⁴<http://omim.org/entry/211980>

Table 3 | KIR gene associations with recurrent spontaneous abortion.

Ethnicity	Number of patients	Number of controls	KIR association	Reference
Greeks	26 Couples	26 Couples	2DL1 + 2DL2 + 2DL3 protective	Varla-Leftherioti et al. (2003)
Greeks	15	15	2DL1 + 2DL2 + 2DL3 protective; 2DL – HLA-C mismatch associated	Varla-Leftherioti et al. (2005)
Cauc. + Mongol.	158	81	No significant results	Varla-Leftherioti et al. (2007)
Chinese	73 Couples	68 Couples	2DL1 + C2 in both partners protective; 2DS1 + C2 in both partners protective	Wang et al. (2007)
Argentina	88 Couples	139 Healthy individ.	AA genotype associated; 2DL2 protective	Flores et al. (2007)
Chinese	16	41	2DL2 associated	Hong et al. (2008)
English Caucasian	95 Females; 67 males	269 Females	Female AA associated; male C2 associated	Hiby et al. (2008)
Brasilian Caucasian	68 Couples	68 Couples	Five to six activating KIRs associated	Vargas et al. (2009)
Poles	91	117	Six inhibitory KIRs associated; six activating KIRs protective	Nowak et al. (2009)
English Caucasian	975 RSA + FGR + PE	592	Female AA associated only when fetus has more C2 than mother	Hiby et al. (2010)
Mixed	224	182	No significant results	Varla-Leftherioti et al. (2010)
Asian Indians	177	200	Maternal 2DL1+ both partners C2C2 protective; 2DS2+ both partners C1C1 associated	Faridi and Agrawal (2011)
Poles	85	117	Female AA C1C2+ partner C2C2 strongly protective	Nowak et al. (2011b)
Turks	40	90	Female AA protective	Ozturk et al. (2012)

and KIR3DL2 had neither stimulating or inhibiting effect on its cytotoxic or interferon-gamma secreting activity (Dorothee et al., 2003). It was also shown that a majority of T cells infiltrating a tumor display T regulatory rather than effector cell phenotype (Esendagli et al., 2008; Schneider et al., 2011). Thus, cells infiltrating malignant areas in NSCLC seem to be poor in KIR expression and cytotoxic activity. Nevertheless, it is conceivable that cytotoxic effector cells, including NK, might eliminate or reduce numbers of potentially metastatic circulating cancer cells, as it has been described for uveal melanoma (Maat et al., 2009).

We typed 269 NSCLC patients for *KIR* and *KIR* ligand genes and compared the results with those of 690 unrelated healthy control individuals, all of them Polish Caucasians. No differences in the distribution of individual *KIR* genes or *AA* and *Bx* genotypes were observed (Wiśniewski et al., 2012). This finding confirms earlier report of Al Omar et al. (2010) in 186 NSCLC cases and 255 controls from England and Northern Ireland. However, we found less frequent prevalence of *HLA-C C1/C2* genotype in patients than in controls, whereas both homozygotes were more frequent in patient group (Wiśniewski et al., 2012). This result was discordant with that of Al Omar et al. (2010), who did not observe any association of *HLA-C C1* and *C2* groups (encoding ligands for KIR2DL2/3 and KIR2DL1, respectively) with NSCLC, but found weak association of *HLA-B Bw4Thr80* (coding for a ligand for KIR3DL1) which lost significance after correction. This was not, however, visible in our study (Wiśniewski et al., 2012). Interestingly, Al Omar et al. (2010) observed a protective effect of *C1/C2* genotype on the prevalence of NSCLC, but only in the presence of *KIR2DL3* gene, which we have not seen.

The reason for seemingly protective effect of *C1/C2* genotype on NSCLC prevalence needs explanation. *HLA-C* molecules play

two distinct roles in cellular immunity: first, they may present antigenic peptides to CD8⁺ T lymphocytes, although this their function seems less important than that of *HLA-A* and *HLA-B*; second, they protect normal cells of the body from the attack of NK cells equipped with *HLA-C*-binding inhibitory receptors such as KIR2DL1, KIR2DL2, and KIR2DL3. *HLA-C* molecules participate also in a process called “NK cell education”: these NK cells which possess inhibitory receptors binding self *HLA* class I molecules, including *HLA-C*, are “allowed” to mature, whereas NK cell clones devoid of such receptors remain immature and inactive (Björkström et al., 2010; Elliott and Yokoyama, 2011; Schönberg et al., 2011). Therefore, we can imagine that in NSCLC patients, individuals with *C1/C2* genotype may have wider repertoire of antigenic peptides, including tumor antigens, presented to their *HLA-C*-restricted CD8⁺ cytotoxic T cells which can eradicate tumor cells. These individuals may also possess wider repertoire of *HLA-C*-educated NK cell clones which would eliminate these tumor cells which lost *HLA-C* expression. Transformed cells relatively frequently lose one *HLA-C* allele (Carretero et al., 2008; Mendez et al., 2009), including loss of heterozygosity in lung cancer (So et al., 2005). In *C1/C1* and *C2/C2* homozygotes, this does not change a sensitivity of cancer cells to NK-mediated lysis because they retain the same *HLA-C* allomorph encoded by the second chromosome and recognized by their mature NK cells. In this respect, *C1/C2* individuals are in a privileged position, because even when a tumor cell retains one *HLA-C* allele, it is still vulnerable to lysis by these NK cells which express KIR recognizing a product of the second allele which had been lost (Maat et al., 2009).

Multivariate analysis revealed an effect of *KIR* and *HLA-C* genotype on the response of our patients to treatment

(surgery and/or chemotherapy): *KIR2DL2+*, *KIR2DS2+*, *C1/C1* individuals responded better to therapy and survived longer than patients with other genotypes (median survival time 23 months versus 10 months for patients with other genotypes; Wiśniewski et al., 2012).

Why the effect of *KIR2DL2* and *KIR2DS2* on treatment response and survival was seen only in the absence of *C2* which is not their ligand (or a major ligand in the case of *KIR2DL2*, see **Table 1**)? Great majority (about 96%) of our patients (and controls as well) possessed *KIR2DL1* gene whose product strongly interacts with *C2*⁺ HLA-C molecules (Parham, 2005; see **Table 1**). Therefore, in *C2*⁺ patients, NK cells expressing *KIR2DL1* would be strongly inhibited and ineffective in *C2*⁺ tumor eradication. In individuals of *KIR2DL2*⁺, *KIR2DS2*⁺, *C1/C1* genotype this interaction is not possible, therefore NK cells may be activated and kill tumor cells. *KIR2DL2* interaction with *C1* is much weaker than that of *KIR2DL1* with *C2* (Parham, 2005), so NK cell activation would not be so strongly inhibited. On the other hand, why *C1/C1* genotype was not protective in the absence of *KIR2DL2* and *KIR2DS2* in our patients, is less clear. Perhaps activating *KIR2DS2* receptor, whose ligand is not known (**Table 1**), is necessary for NK cell-mediated tumor cell lysis in this setting, but NK cells are not sufficiently inhibited by a weak *KIR2DL2*-*C1* interaction. It is also possible that in some circumstances, e.g., when HLA-C *C1* molecules are filled with a proper peptide, *KIR2DS2* molecule may bind them strongly enough to activate the cell.

Our results suggest that NSCLC patients possessing *KIR2DL2* and *KIR2DS2* genes but not having *C2* ligand for *KIR2DL1* may respond better to treatment and survive longer than individuals bearing other genotypes. We also indicate that *C1/C2* genotype may give some protection from the initiation of this tumor.

VIRAL INFECTIONS

Viruses infect cells and replicate inside them, forcing cell metabolism to produce abundant amounts of viral proteins. These are degraded to oligopeptides, bound by HLA class I molecules and presented to cytotoxic T cells (CD8⁺) like all other proteins produced within the cell (Neeffjes et al., 2011). Therefore, many viruses evolved molecular mechanisms which interfere, in different ways, with cell surface expression of HLA class I molecules (Horst et al., 2011). This makes a virus-producing cell resistant to cytotoxic activity of T cells. On the other hand, the lack of one or all HLA class I molecules makes it susceptible to lysis by NK cells. This, however, depends on the repertoire of KIRs expressed on NK cell clones, which, in turn, depends on *KIR* genotype of the given individual (Parham, 2005; van Bergen and Koning, 2010). Associations of several types of viral infections and resulting human diseases with *KIR* genes have already been studied. Detailed review of the results of these studies would go beyond the acceptable volume of this article, therefore I will only mention here most important findings.

1. HIV-1 infection results in slower progression to AIDS in individuals possessing *KIR3DS1* gene and *HLA-Bw4* variant encoding isoleucine residue in position 80 (Martin et al., 2002a). This discovery stimulated multiple studies which are a topic of recent review (Koerner and Altfeld, 2012).

2. HIV-2 was much less extensively studied, because its prevalence is limited to West Africa, and its infection is more benign than that of HIV-1. No strong correlation with any *KIR* gene (including *KIR3DS1*) was observed, except for a trend for protective effect of *KIR2DL2/KIR2DS2/C1* genotype (Yindom et al., 2010).
3. Both protective and detrimental effects of *KIR2DL2* on human T-lymphotropic myelopathy/tropical spastic paraparesis in Japan, depending on HLA allele (Seich al Basatena et al., 2011).
4. Several *KIR* genes were found to be associated with H1N1 influenza 2009 pandemics (La et al., 2011; Aranda-Romo et al., 2012).
5. Mean number of activating *KIRs* per genotype was lowest in survivors of Ebola virus infection and highest in those with fatal outcome (Wauquier et al., 2010).
6. In human papillomavirus (HPV)-induced cervical intraepithelial neoplasia, protective effect of *KIR3DL1* and *KIR2DL1* in the presence of their ligands, and increased risk associated with *KIR3DS1* was observed in Puerto Ricans and North Americans (Carrington et al., 2005), whereas only protection by *KIR2DL5B* was found in Swedish sample (Arnheim et al., 2005). In another HPV-induced disease, recurrent respiratory papillomatosis, *KIR3DS1* together with *KIR2DS1* appeared protective (Bonagura et al., 2010).
7. In HCMV infection of chronic hepatitis (Hepatitis B virus- or hepatitis C virus-induced) an expansion of NKG2C⁺ NK cells selectively expressing *KIR2DL2* or *KIR2DL3* was described (Beziat et al., 2012). In vasculitis complication of RA, CD4⁺CD28⁻ T cells were observed only in patients infected with HCMV, suggesting a role for HCMV in boosting T cell autoreactivity (van Bergen and Koning, 2010).
8. Hepatitis B virus infection is common worldwide, particularly in China where it is a cause of the highest frequency of hepatocellular carcinoma (HCC) in the world (Zidan et al., 2012). A synergistic effect of a combined genotype *C1C1*⁺/*Bw4-80I*⁺/*KIR2DS4fl*⁺/*KIR2DS4del*⁺ on HCC risk was observed (Pan et al., 2011).
9. The role of *KIR* genes and molecules in HCV infection and HCV-induced HCC was so extensively studied that covering this topic would require a separate article. The protection from low-dose (injection or needle stick) but not from high-dose HCV infection was first described by Khakoo et al. (2004) in British Caucasoids and Afroamericans. The regulation of HCV infection by NK cells was briefly reviewed recently by Brenndörfer and Sällberg (2012).

GENERAL REMARKS

The role of polymorphic NK cell receptors, KIRs, recognizing even more polymorphic HLA class I molecules, in human health and disease is gaining a constantly growing interest, and the number of publications is growing exponentially. This review could have touched only a fragment of this field.

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