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

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INTRODUCTION

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

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1 http://www.allelefrequencies.net/diseases/dis0012.asp
Table 1 | Ligands of KIR molecules (based on Kuśnierzcyk, 2006; Graef et al., 2008; 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*01,03,07,08,12,13,14,02,1507,1601; HLA-B46. C2 (Lys80) – C*02,04,05,06,0702,12042,1401,150(without 1507),1602,17.

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

SKIN DISEASES: PSORIASIS AND ATOPIC DERMATITIS

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*07 and HLA-Cw*0002), 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; 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).
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 | 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  | Jobin et al. (2006)    |
| 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       | 0.0565 | 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) |

*If 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 KIR2DS1 gene in different subpopulations of T and/or NK cells.

This, 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 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.
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 placenta. 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 heterotrimers (Hiby et al., 2010). 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 FcRγy 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 KIR3DPR1 (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). 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; Kiesling 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 role. In NSCLC, NK cells infiltrate rather peritumoral than tumor tissue, in contrast to T lymphocytes (Esenagli et al., 2008; Schneider et al., 2011), and these NK cells which do infiltrate the tumor are predominantly CD56bright, negative for NK cell receptors (including KIRs), and exhibit low cytotoxic activity ex vivo (Carrega et al., 2008; Esenagli 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,

http://omim.org/entry/211980

http://www.allelefrequencies.net/
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) |
| Cau. + 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 | Hibi 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 | Novak et al. (2009) |
| English Caucasian | 975 RSA + FGR + PE | 592                 | Female AA associated only when fetus has more C2 than mother | Hibi 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 | Novak 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 (Dorothée 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 whom 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 loose 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.
Kuśnierzcyk

KIR gene associations with diseases

(a) 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 T cells (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 (Neefjes 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 NK2G2+ 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+/KIR2DS4+/KIR2DS4+/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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