Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Deep Insight Section

NK cell receptors: evolution and diversity

Gwenoline Borhis, Salim I Khakoo

Department of Hepatology, Division of Medicine, Imperial College London, UK (GB, SIK)

Published in Atlas Database: February 2011

Online updated version : http://AtlasGeneticsOncology.org/Deep/NKCellRecEvoDivID20095.html
DOI: 10.4267/2042/46021

Summary

Natural Killer cell functions are regulated by combinations of activating and inhibitory receptors, derived from a number of different gene families. This review focuses on receptors for MHC class I, which include the killer cell immunoglobulin-like receptors (KIR) and the CD94:NKG2 family of receptors. In particular the KIR are diverse and rapidly co-evolving with their classical MHC class I ligands. Thus NK cells are part of the innate immune system that are continuing to adapt to the challenges of pathogens.

Introduction

NK cells are an important component of the innate immune system, which participate in the early immune defence against intracellular pathogens and tumour transformation. They were originally defined by their ability to spontaneously eliminate rare cells lacking expression of class I Major Histocompatibility Complex (MHC class I) self molecules, a process commonly referred to as "missing self" recognition (Biron et al., 1999; Purdy and Campbell, 2009).

Upon activation, NK cells can mediate direct cytotoxicity or secrete cytokines and chemokine that modulate subsequent steps in the adaptive immune response. These functions are regulated by the combination of signals from activating and inhibitory receptors (Lanier, 1998). The MHC class I receptors are particularly important for NK cells to discriminate "self" (healthy cells) from "altered-self" (infected- and transformed-cells) or "missing self". MHC class I receptor:ligand interactions can induce inhibitory signals that counteract activating receptor signals and lead to NK cell inhibition. In contrast down-regulation or loss of MHC class I expression, during viral infection or carcinogenesis, shifts the balance towards NK cell activation and target cell destruction by removing this inhibitory signal. Thus in health NK cells are tolerant towards host cells, but in disease this tolerance can be readily broken.

MHC class I receptors on NK cells

MHC class I receptors on NK cells can be either inhibitory or activating. The inhibitory receptors for MHC class I regulate NK cell function by generating a tonic inhibitory signal as hypothesized in the "missing-self" model (Ljunggren and Karre, 1990). The role of the activating receptors for MHC class I appears less clear, but genetic studies have implicated them in recognition of virally infected cells.

Several inhibitory receptors have been identified, but there are two main families involved in NK regulation by MHC class I: the Killer cell Immunoglobulin-like Receptors (KIR) and the C-type lectin-like CD94/NKG2A heterodimers. KIR interact with the classical MHC class Ia (HLA-A, -B and -C) while CD94/NKG2A recognizes the non-classical MHC class Ib, HLA-E. Both synergize and permit NK cells to sense and respond to changes in MHC class I expression. These receptors are expressed in a combinatorial fashion on NK cells to generate an NK cell repertoire. The importance of this is gradually being realised. Expression of an MHC class I inhibitory receptor appears to confer additional reactivity on these NK cells, a phenomenon originally termed "licensing" (Kim et al., 2005). Thus NK cells without inhibitory receptors for MHC class I are thought to be relatively hypofunctional, although in specific scenarios, these cells can become important for viral eradication as shown by studies in murine CMV infection (Orr et al., 2010). Furthermore in disease states in which a specific inhibitory receptor may be beneficial, such as KIR2DL3 in hepatitis C virus infection, then individuals with more beneficial repertoires may be more likely to clear infection (Alter et al., 2010).

In addition to these key receptors, members of the Ig-Like Transcripts (ILTs) family, which are genetically related to KIR (Wilson et al., 2000), can also recognize

MHC class I. For example, LILRB1 (LIR-1, ILT-2), which binds a broad range of MHC class I molecules including HLA-G (Vitale et al., 1999), is able to inhibit the NK cell line NK92 (Kirwan and Burshtyn, 2005). It is also expressed in a variegated fashion on NK cells (Davidson et al., 2010). However it does not appear to play a part in NK cell education and it has yet to be demonstrated that this gene family play a major role in inhibiting NK cells *in vivo* (Yawata et al., 2008).
CD94/NKG2A and KIR molecules have adopted two different recognition strategies. To a large extent CD94/NKG2A ignore MHC class I diversity by recognizing HLA-E. This non-polymorphic MHC class I molecule binds leader peptide sequences derived from classical MHC-A, -B and -C molecules and also from HLA-G (Llano et al., 1998). In contrast the KIR family embrace the diversity of MHC class I through direct recognition of polymorphic determinants. This strategy leads to a highly variable and polymorphic KIR system with diversity comparable to that of MHC class I (Valiante et al., 1997a).

KIR structure and signalling function

The KIR family (assigned the designation of CD158) is a member of the immunoglobulin superfamily that comprises 15 expressed receptors (KIRDL1-5B, KIR3DL1-3, KIR2DS1-5 and KIR3DS1): which can be either inhibitory or activating (Table 1). All KIR are type I transmembrane glycoproteins formed from either two (KIR2D) or three (KIR3D) extracellular Ig-like domains, a stem region, a transmembrane region and a cytoplasmic tail. Depending on the length of the cytoplasmic tail KIR can be subdivided into long-tailed and short-tailed receptors. In general these structural characteristics correlate with their function. Long-tailed KIR are generally inhibitory and short-tailed KIR are activating (Vilches and Parham, 2002). An exception to this rule is the receptor KIR2DL4 which has a long intracytoplasmic tail but stimulates potent cytokine production, although only minimal cytotoxicity (Rajagopalan et al., 2006).
Inhibitory KIR contain one or two Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs; V/I/LxYxxL/V), which are require for NK cell inhibition via recruitment of the protein tyrosine phosphatases SHP-1 and SHP-2. SHP-1/2 activation leads to the suppression of activating receptor signals (Long, 2008). Activating KIR possess a positively charged residue (usually arginine) in the transmembrane region, which facilitate the association with accessory molecules, DAP12 or FcεRIγ (KIR2DL4) and NK cell activation (cytotoxicity and/or cytokine production) (MacFarlane and Campbell, 2006). The exception, KIR2DL4 contains both ITIMs and a positively charged residue (lysine), which facilitates the association with FcεRIγ and the induction of the activating signals (Kikuchi-Maki et al., 2005).

The KIR genes can be divided into six lineages based on phylogenetic analysis. This has allowed "tracking" of the KIR across species and given insights into the evolution of the KIR gene families. Lineage I KIR have two extracellular domains in the D0D2 conformation; lineage II KIR are specific for MHC-A and -B; lineage III KIR bind HLA-C; lineage V KIR are related to the human KIR framework gene KIR3DL3; and lineage IV and VI KIR are expansions specific to the rhesus macaque and new world monkeys respectively.

KIR locus and diversity

Genotyping of individuals for specific KIR genes demonstrated an unexpected diversity in gene content amongst the population (Uhrberg et al., 1997). The genotype of these individuals correlated with expression of KIR genes thus demonstrating that this genetic diversity would be important for NK cell function. This seminal study started a detailed investigation into KIR genetics. Sequencing of two KIR haplotypes from a single individual showed that the KIR are encoded by a compact family of genes which occupy about 150 kb of the Leukocyte Receptor Complex (LRC) on chromosome 19q13.4 (Wilson et al., 2000; Wende et al., 1999). The locus is flanked by the *LILR* and the *FCAR* genes and contains up to 17 *KIR* genes and pseudogenes (Kelley et al., 2005). Because the KIR genes have high sequence homology to each other (90-95%) and are closely distributed within the LRC, they have been proposed to evolve by non-allelic homologous recombination (Carrington and Cullen, 2004). This mechanism could explain the expansion and contraction of the *KIR* locus and provide a basis for the substantial diversity observed (Hsu et al., 2002a; Hsu et al., 2002b; Shilling et al., 2002; Uhrberg et al., 2002; Whang et al., 2005; Martin et al., 2003).
Haplotypic diversity
The number of putatively expressed *KIR* genes usually ranges from 7 to 12, depending primarily on the presence or absence of activating *KIR* loci (Wilson et al., 2000; Uhrberg et al, 2002; Witt et al., 1999). This variation in gene content is one component of KIR diversity. Despite this extreme variability some systematic features are conserved in the organisation of the KIR locus. Four KIR genes, *KIR3DL3*, *KIR3DP1*, *KIR2DL4* and *KIR3DL2*, are found in all individuals and have been named framework loci (Bashirova et al., 2006). *KIR3DL3* and *KIR3DL2* define the ends of the KIR-gene region and *KIR3DP1-KIR2DL4*, the middle. Regions of genetic variability are located between *KIR3DL3* and *KIR3DP1*, and between *KIR2DL4* and *KIR3DL2* (Wilson et al, 2000; Martin et al., 2000).
Two distinct forms of haplotype, termed A and B, can be distinguished on the basis of gene content. Haplotype A has a fixed gene content (*KIR2DL1, KIR2DL3, KIR2DL4, KIR2DS4, KIR3DL1, KIR3DL2, KIR3DP1* and *KIR3DL3*) (Uhrberg et al., 1997) and fewer genes than B haplotype but the most functionally relevant distinction between these two haplotypes is the

number of activating receptors. Haplotype A contains only a single activating KIR gene, *KIR2DS4*, whereas haplotype B contains various combinations of *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS5*, *KIR3DS1* and *KIR2DS4*. Furthermore, the *KIR2DS4* gene has a null allele with a population frequency of about 84% (Maxwell et al., 2002), thus some homozygous A haplotype individuals don't express any activating KIR (Hsu et al., 2002b). Although A haplotypes are fixed in term of the number and type of genes present, they show extensive allelic variation at several of the genes. In contrast to A haplotype, B haplotype displays a much greater variety of gene contents. Based on segregation analysis, more than 20 different B haplotypes have been described (Hsu et al., 2002a; Yawata et al., 2002a). These haplotypes contain various combinations of KIR genes, including several activating KIR but there is a very high linkage disequilibrium (LD) between many pairs of genes, as *KIR2DL1/KIR2DL3* or *KIR3DL1/KIR3DL2* alleles (Uhrberg et al., 1997; Shilling et al., 2002; Witt et al., 1999; Norman et al., 2002; Norman et al., 2001; Toneva et al., 2001; Crum et al., 2000).

However despite the broad categorizations, there are several exceptions to these simple rules. For instance despite the fact that KIR3DL1 (inhibitory) and KIR3DS1 (activating) segregate as alleles of a single locus in the vast majority of individuals, haplotypes have been described in which they occur on the same chromosome (Martin et al., 2008; Norman et al., 2009). Similarly some KIR haplotypes have fewer than expected KIR. For instance a recently described haplotype contains only 3 KIR genes KIR3DL3, KIR2DS1 and KIR3DL2 (Traherne et al., 2010). Thus the rules for the KIR locus appear unusually flexible, perhaps due to the combination of a high sequence homology between the genes, and an overlap in function of these receptors with the well conserved CD94:NKG2 family of receptors. Furthermore some genes (KIR2DS3 and KIR2DS5) appear to occur in two different chromosomal locations. This has led to the splitting of the locus into two separate sections a centromeric section (KIR3DL3-KIR3DP1) and a telomeric section (KIR2DL4-KIR3DL2) which appear to have diversified independently (Pyo et al., 2010). Sequence analysis of a number of KIR haplotypes shows that allelic diversity of the centromeric section is predominant in the A haplotypes, but it is in the telomeric section of the B haplotypes that allelic diversity is most noticeable.

The distribution of A and B haplotypes varies widely between distinct ethnic groups. The A and B haplotype frequencies are relatively even in Caucasian populations (Uhrberg et al., 1997; Hsu et al., 2002b). However the A haplotype dominates in the Korean, Japanese and Han Chinese populations with an approximate 75% frequency (Whang et al., 2005; Yawata et al., 2002b; Jiang et al., 2005) as compared to the Australian Aborigines, who have a very low frequency of the A haplotypes of about 13% (Toneva et al., 2001). These differences may reflect both founder effects and selection by pathogens and may account for some variation in worldwide disease susceptibility.

Allelic polymorphism

Point mutation and homologous recombination generate allelic polymorphism (Table 1) (Norman et al., 2009; Shilling et al., 1998). This allelic polymorphism gives an additional dimension to *KIR* diversity in that unrelated individuals are unlikely to have identical KIR alleles, similar to the situation for MHC diversity (Gardiner et al., 2001). Allelic polymorphism has been described for all the inhibitory *KIR* genes and names for alleles at several of the most polymorphic loci have been specified based on nomenclature used for HLA loci (Shilling et al., 2002). This polymorphism significantly influences their ligand affinities and levels of cell surface expression. For example, distinct alleles of *KIR3DL1*, one of the most polymorphic KIR genes encode molecules that appear to be expressed at different levels on the surface of NK cells (Gardiner et al., 2001; Yawata et al., 2006; Pando et al., 2003). Moreover this allelic variability can occur at positions encoding residues that affect interaction with HLA class I (Boyington et al., 2000; Fan et al., 2001) and influences both the binding affinity and the inhibitory capacity. Similarly the genes KIR2DL2 and KIR2DL3 also segregate as alleles of a single locus and although they have broadly similar MHC class I specificity, bind their ligands with substantially different avidities (Moesta et al., 2008). The synergy of haplotype variability and, allelic polymorphism has generated substantial diversity across both individual populations, but also across different ethnic groups (Rajalingam et al., 2001). This diversity is likely driven by both encounters with pathogens, but also by reproductive fitness.

Table 1: KIR nomenclature, lineages and ligands(IPD - KIR Database; Cadavid and Lun, 2009)

Gene name	CD nomenclature	No. of alleles	No. of protein	Lineage	Ligand(s)	Function
KIR2DL1	CD158a	43	24	III	HLA-C2	inhibitory
KIR2DL2	CD158b1	29	12	III	HLA-C1 (weakly HLA-C2)	inhibitory
KIR2DL3	CD158b2	33	17	III	HLA-C1 (weakly HLA-C2)	inhibitory
KIR2DL5A*	CD158f	45	18	I	Unknown	inhibitory
KIR2DL5B*				I	Unknown	inhibitory

KIR3DL1	CD158e1	74	58	II	HLA-B^{Bw4} and HLA-A^{Bw4}	inhibitory
KIR3DL2	CD158k	84	62	II	Certain HLA-A3 and HLA-A*11	inhibitory
KIR3DL3	CD158z	107	56	V	Unknown	inhibitory
KIR2DL4	CD158d	47	22	I	HLA-G	activating
KIR2DS1	CD158h	15	7	III	HLA-$C2^{A}$	activating
KIR2DS2	CD158j	22	8	III	Potentially HLA-C1 (binding not detectable)	activating
KIR2DS3		14	5	III	Potentially HLA-C1	activating
KIR2DS4	CD158i	30	13	III	HLA-Cw4 and HLA-11	activating
KIR2DS5	CD158g	15	10	III	Unknown	activating
KIR3DS1	CD158e2	16	12	II	Potentially HLA-B^{Bw4} (binding not detectable)	activating
KIR2DP1		22	0	III	/	pseudogene
KIR3DP1	CD158c	23	0	V	/	pseudogene

*KIR2DL5 gene is duplicated and encoded by two separate loci within the LRC gene cluster.

KIR recognition and peptide selectivity

Individual KIR recognize distinct subsets of the classical human MHC class I allotypes. This binding specificity is determined both by residues of the MHC class I and those of the peptide bound by the MHC class I molecule. Inhibitory KIR are able to recognize all the known HLA-C allotypes (C1 and C2 subgroup) and some subsets of HLA-A and HLA-B allotypes. KIR2DL1 binds HLA-C2 allotypes, which all have a lysine at position 80 (Colonna et al., 1993). KIR2DL2 and KIR2DL3, which segregate as alleles of the same locus, bind mainly HLA-C1 allotypes (with an asparagine at position 80), some HLA-C2 allotypes and a few HLA-B allotypes which have an asparagine at position 80 and also a valine at position 76 (Moesta et al., 2008; Wagtmann et al., 1995; Pende et al., 2009). KIR3DL1 recognize the "Bw4" motif present in 40% of the known HLA-B allotypes and in some HLA-A allotypes, with a higher affinity for the Bw4 motifs containing an isoleucine at position 80 (Cella et al., 1994; Gumperz et al., 1995). KIR3DL2 is only known to bind HLA-A3 and HLA-A11 allotypes whilst ligands for KIR2DL5 and KIR3DL3 have not yet been identified.

Given the high sequence homology between the extracellular domains of some activating and inhibitory KIR (~99%), several activating KIR have been reported to bind the same HLA molecules as their inhibitory counterparts, although with significantly weaker affinity (Biassoni et al., 1997; Valés-Gómez et al., 1998; Stewart et al., 2005). Due to their low affinities, the activating KIR-HLA binding specificity is quite uncertain. Moreover the KIR-HLA affinities can be enhanced by specific peptides presented in the HLA molecules, as has been shown for KIR2DS1 interactions with Epstein-Barr virus-infected cells (Stewart et al., 2005). One potential model is that these receptors may bind specific viral peptides that have yet to be determined.

In addition to the MHC class I heavy chain, all inhibitory KIR tested to date have some degree of peptide selectivity (Boyington et al., 2000; Malnati et al., 1995; Rajagopalan and Long, 1997; Hansasuta et al., 2004). This appears to have a functional relevance in that NK cells expressing KIR2DL3 are exquisitely sensitive to the peptide bound by MHC class I. This is because peptides that stabilise MHC class I, but bind KIR weakly can antagonize the inhibition due to MHC class I:peptide complexes that bind KIR strongly (Fadda et al., 2010). This process appears to be more efficient than MHC class I downregulation in activating NK cells, and may be important for recognition of infected targets (Rajagopalan and Long, 2010).

KIR evolution

A comparison of the KIR genes in human and chimpanzees revealed unexpectedly rapid evolution of the KIR locus, in many ways exceeding the pace of their MHC class I ligand (Khakoo et al., 2000). This contrasts with the high conservation of the CD94:NKG2A system (Shum et al., 2002). Work in the higher primates has revealed that in these species the KIR genes have expanded substantially. Mice, which are the most frequently used immunological model for the immune system of man and his response to disease, do not have KIR as regulators of NK cell activity (Figure 1). Instead they have an expansion of the C-type lectin-like receptors, the Ly49 genes which also bind classical MHC class I molecules. These genes are related to the NKG2A family of receptors, and both these gene families in addition to the CD94 gene are found on murine chromosome 6 in a region designated

the natural killer cell complex (NKC) (Vance et al., 1998). In mice CD94:NKG2A binds the non-classical MHC class I molecule Qa-1, which also binds MHC class I leader sequences. Thus comparison of humans and rodents has revealed two distinct evolutionary pathways for NK cell receptors: one leading to diversification of KIR and the other to diversification of Ly49. Both species have inhibitory NK cell receptors for classical class I molecules and both for a non-classical MHC class I molecule, although NKG2A in mouse and human are not strictly orthologous. Remnants of non-functional genes can be found in the alternate species: the KIR are represented by a gene on murine chromosome X and Ly49 is a pseudogene in humans (Kelley et al., 2005) (Figure 1).

Studies in other species have revealed the uniqueness of KIR in the simian primates. KIR genes have been found in species as diverse as cattle, horses, dogs and pinnipeds (Parham et al., 2010). These are thought to have derived from duplication of an ancestral KIR3D gene over 100 million years ago. This resulted in two genes: KIR3DL and KIR3DX (Guethlein et al., 2007). The KIR3DL gene is thought to have spawned the KIR genes of the primates, and the KIR3DX gene given rise to the multigene KIR family in cattle (Sambrook et al., 2006). KIR3DX is retained in humans, however it is a non-functional pseudogene in the LRC amongst the LILR gene. The adoption of different solutions to the issue of NK cell receptor variability is further illustrated by the expansion of the NKG2 family of genes in the prosimians (Averdam et al., 2009) and the observation that the pinnipeds (seals and sea lions) seem to cope with having only one functional KIR and one functional Ly49 gene (Hammond et al., 2009).

Genetic studies implicating specific combinations of KIR in infectious diseases imply that pathogens are a major driving force in KIR evolution. This follows naturally from the observation that natural killer cells are important in clearing viral infections. Pathogens can drive KIR selection both by a direct effect on specific KIR genes and also via an indirect selective pressure through driving the evolution of MHC Class I. This is well illustrated by the co-evolution of KIR and the MHC-C locus in the great apes. The KIR can be divided into lineages based on sequence homologies. The lineage III KIR have MHC-C ligands. The most divergent species from man with an MHC-C allele is the orangutan (Adams et al., 1999). In this species this locus is present in only about half the individuals. Nevertheless, in the orangutan and man's more closely related ancestors

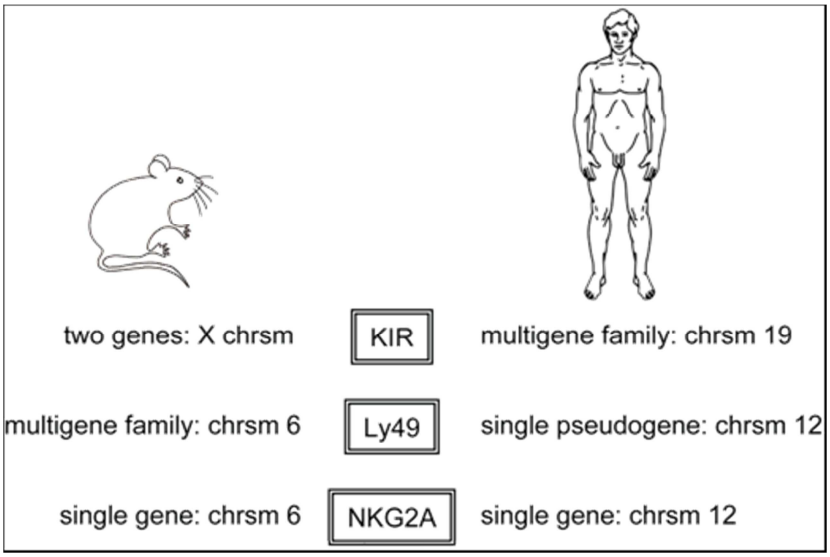

Figure 1

(the gorilla, the common chimpanzee and the pygmy chimpanzee) lineage III KIR have expanded, implying that MHC and the KIR are co-evolving (Abi-Rached et al., 2010b). Similarly in the old world monkeys the expansion of MHC-A/B locus has led to expansion of lineage II KIR, and in the hoolock gibbon loss of MHC-G corresponds to loss of the lineage I gene KIR2DL4, which has been shown to be relatively conserved amongst higher primates (Abi-Rached et al., 2010a; Parham et al., 2010).

Whilst humans and chimpanzees share MHC-A, -B and -C loci, they share relatively few KIR genes. These include the framework genes KIR3DL3, KIR2DL4 and KIR3DL2 (which in the chimpanzee is a chimera of human KIR3DL1 and KIR3DL2 called *Pt*-KIR3DL1/2), and the genes KIR2DL5 and KIR2DS4 (Khakoo et al., 2000). Humans have retained lineage III inhibitory KIR which bind strongly to HLA-C, however the activating KIR for HLA-C are low avidity. Conversely the common chimpanzee has retained high avidity activating and inhibitory for both group 1 and group 2 HLA-C allotypes. Furthermore, although the lineage II human KIR bind both HLA-A and -B allotypes, the most relevant interaction appears to be that of KIR3DL1 with HLA-B allotypes with the Bw4 serological motif. Although this KIR does bind HLA-A

allotypes with the same serological motif. The binding of other KIR to HLA-A allotypes is less well documented. KIR3DL2 binds HLA-A3 and HLA-A11, although the avidity of this interaction is not well studied (Dohring et al., 1996; Pende et al., 1996; Valiante et al., 1997b). It has also been shown to bind tetramers of HLA-B27 homodimers (Kollnberger et al., 2007). KIR2DS4 also binds HLA-A11 (Graef et al., 2009). However the functional relevance of these interactions with HLA-A is not as well documented as for HLA-B: and KIR. Conversely *Pt*-KIR3DL2, binds both MHC-A and -B allotypes, and can demonstrably inhibit chimpanzee NK cells in a manner not restricted by the Bw4 serological motif, even though this motif is present on a number of chimpanzee MHC-B allotypes (Khakoo et al., 2002). Thus even where the most simple motifs for KIR binding on MHC appear relatively conserved between species there is substantial evidence for a more rapid evolution at the KIR locus.

Within different human populations there is a great diversity in the frequencies of individual KIR genes (Gonzalez-Galarza et al., 2011). The essential role for unequal crossing over in generating this diversity is illustrated by in depth study of the KIR3DL1/KIR3DS1 locus in which it has been demonstrated that this process can account for both duplication and deletion within the KIR gene complex (Norman et al., 2009). Further selection may occur on the basis of the interaction of KIR with its MHC class I ligands, to maintain a functional relationship and which may be fine tuned by the affinity of the KIR for its MHC class I ligand (Single et al., 2007). Thus in the Yucpa population there is a relatively high frequency of the "strong educating" HLA-C*07 allele, and correspondingly higher frequencies of KIR2DL3 alleles with low avidities for HLA-C (Gendzekhadze et al., 2009). This implies that evolutionary pressures have combined to ensure that inhibitory signals to NK cells can be easily overcome and so NK cells can be readily activated in response to pathogens.

Impact of KIR diversity on Human health and disease

The impact of KIR diversity on human health is well illustrated by disease association studies. Whilst infection is thought to be the major driving force for the evolution of KIR, there is substantial evidence that KIR diversity impacts a number of pregnancy associated disorders, including pre-eclampsia and recurrent spontaneous abortion (Moffett-King, 2002). During placentation the trophoblast burrows into the placenta, and natural killer cells appear to be important for this process. Analysis of maternal and foetal KIR and MHC class I genotypes demonstrate that if these result in greater foetal NK cell activation then pregnancy is more likely to be successful, due to improved placentation. Thus in cases where the KIR haplotype of the fetus has a preponderance of activating receptors, such as a type B KIR haplotype, then there I a lower probability of pre-eclampsia (Hiby et al., 2004). Conversely if the fetus has only one activating KIR, as is found in a group A KIR haplotype and the mother has a strong inhibitory MHC class I type for example two group 2 HLA-C alleles then there is a greater risk of pre-eclampsia, foetal growth retardation and recurrent spontaneous abortion (Hiby et al., 2010). This likely drives the evolution of the KIR locus towards a preponderance of activating receptors.

Early studies in infectious disease would concur with this evolutionary direction. In HIV infection the activating receptor KIR3DS1 and its HLA-B ligands Bw4 with isoleucine at position 80 (Bw4^{80I}) are associated with a slower progression to AIDS (Martin et al., 2002). This begs the question as to the persistence of the "inhibitory" A haplotypes in the human population. Further studies of HIV infection have revealed a second model in which a hierarchy of inhibitory interactions between the inhibitory receptor KIR3DL1 and its HLA-B^{Bw4} ligands influences the progression to AIDS (Martin et al., 2007). Interestingly in this genetic analysis the most protective allele KIR3DL1*004 is one which is not expressed on the cell surface (Pando et al., 2003). This is a feature of other KIR alleles, including KIR2DL2*004 and a number of alleles of KIR2DS3 (VandenBussche et al., 2006; VandenBussche et al., 2009). This implies that care must be taken with the interpretation of these genetic analyses as the presence of the receptor and its ligand does not necessarily mean that there is a simple functional relationship.

The importance of inhibitory receptor:ligand interactions is probably best illustrated by consideration of hepatitis C virus (HCV) infection. This is a positive stranded RNA virus that has relatively little specific effects on MHC class I expression, and so may act as a more general template for understanding the role of NK cells in viral infection. Genetic analysis has shown that weaker inhibitory interactions are associated with a more beneficial outcome of HCV infection. It was originally shown that KIR2DL3 and its group 1 HLA-C ligands were associated with spontaneous resolution of HCV infection, which in the vast majority of individuals leads to chronic infection (Khakoo et al., 2004). Binding analysis reveals that KIR2DL3 is a weaker binder to HLA-C than its allele KIR2DL2, which has a similar MHC class I specificity (Winter et al., 1998). It is therefore thought that a weaker inhibitory receptor:ligand interaction can be more easily perturbed than a strong one and hence is more likely to lead to NK cell activation. This protection has been observed in other HCV exposed cohorts and disease settings, including in the clinically important treatment setting (Romero et al., 2008; Knapp et al. 2010; Vidal-Castiñeira et al., 2010). Furthermore, similar to HIV, it can be mapped to the allelic level, but in this case at the HLA-C locus. Thus the common group 1 HLA-C*07 alleles are not protective whereas

most other group 1 HLA-C alleles are protective in combination with KIR2DL3 (Knapp et al., 2010). Thus it appears that there is a balancing selection on the KIR "A" and "B" haplotypes in humans which has permitted maintenance of both in the extant human populations (Gendzekhadze et al., 2009).

Conclusion

By virtue of the expression of KIR, natural killer cells are a branch of the innate immune system that are undergoing constant evolution in response to both pathogens and the challenge of successful reproduction. The KIR have diversified in response to MHC driven selective pressures, following exposure to pathogens. Due to the independent segregation of KIR and their MHC class I ligands, in any given individual some KIR may be redundant. Nevertheless, on a population level, by fine tuning natural killer activity these receptors are key regulators of the innate immune response to pathogens.

References

Ljunggren HG, Kärre K. In search of the 'missing self': MHC molecules and NK cell recognition. Immunol Today. 1990 Jul;11(7):237-44

Colonna M, Borsellino G, Falco M, Ferrara GB, Strominger JL. HLA-C is the inhibitory ligand that determines dominant resistance to lysis by NK1- and NK2-specific natural killer cells. Proc Natl Acad Sci U S A. 1993 Dec 15;90(24):12000-4

Cella M, Longo A, Ferrara GB, Strominger JL, Colonna M. NK3-specific natural killer cells are selectively inhibited by Bw4-positive HLA alleles with isoleucine 80. J Exp Med. 1994 Oct 1;180(4):1235-42

Gumperz JE, Litwin V, Phillips JH, Lanier LL, Parham P. The Bw4 public epitope of HLA-B molecules confers reactivity with natural killer cell clones that express NKB1, a putative HLA receptor. J Exp Med. 1995 Mar 1;181(3):1133-44

Malnati MS, Peruzzi M, Parker KC, Biddison WE, Ciccone E, Moretta A, Long EO. Peptide specificity in the recognition of MHC class I by natural killer cell clones. Science. 1995 Feb 17;267(5200):1016-8

Wagtmann N, Rajagopalan S, Winter CC, Peruzzi M, Long EO. Killer cell inhibitory receptors specific for HLA-C and HLA-B identified by direct binding and by functional transfer. Immunity. 1995 Dec;3(6):801-9

Döhring C, Scheidegger D, Samaridis J, Cella M, Colonna M. A human killer inhibitory receptor specific for HLA-A1,2. J Immunol. 1996 May 1;156(9):3098-101

Pende D, Biassoni R, Cantoni C, Verdiani S, Falco M, di Donato C, Accame L, Bottino C, Moretta A, Moretta L. The natural killer cell receptor specific for HLA-A allotypes: a novel member of the p58/p70 family of inhibitory receptors that is characterized by three immunoglobulin-like domains and is expressed as a 140-kD disulphide-linked dimer. J Exp Med. 1996 Aug 1;184(2):505-18

Biassoni R, Pessino A, Malaspina A, Cantoni C, Bottino C, Sivori S, Moretta L, Moretta A. Role of amino acid position 70 in the binding affinity of p50.1 and p58.1 receptors for HLA-Cw4 molecules. Eur J Immunol. 1997 Dec;27(12):3095-9

Rajagopalan S, Long EO. The direct binding of a p58 killer cell inhibitory receptor to human histocompatibility leukocyte antigen (HLA)-Cw4 exhibits peptide selectivity. J Exp Med. 1997 Apr 21;185(8):1523-8

Valiante NM, Lienert K, Shilling HG, Smits BJ, Parham P. Killer cell receptors: keeping pace with MHC class I evolution. Immunol Rev. 1997 Feb;155:155-64

Valiante NM, Uhrberg M, Shilling HG, Lienert-Weidenbach K, Arnett KL, D'Andrea A, Phillips JH, Lanier LL, Parham P. Functionally and structurally distinct NK cell receptor repertoires in the peripheral blood of two human donors. Immunity. 1997 Dec;7(6):739-51

Uhrberg M, Valiante NM, Shum BP, Shilling HG, Lienert-Weidenbach K, Corliss B, Tyan D, Lanier LL, Parham P. Human diversity in killer cell inhibitory receptor genes. Immunity. 1997 Dec;7(6):753-63

Lanier LL. NK cell receptors. Annu Rev Immunol. 1998;16:359-93

Llano M, Lee N, Navarro F, García P, Albar JP, Geraghty DE, López-Botet M. HLA-E-bound peptides influence recognition by inhibitory and triggering CD94/NKG2 receptors: preferential response to an HLA-G-derived nonamer. Eur J Immunol. 1998 Sep;28(9):2854-63

Shilling HG, Lienert-Weidenbach K, Valiante NM, Uhrberg M, Parham P. Evidence for recombination as a mechanism for KIR diversification. Immunogenetics. 1998 Nov-Dec;48(6):413-6

Valés-Gómez M, Reyburn HT, Erskine RA, Strominger J. Differential binding to HLA-C of p50-activating and p58-inhibitory natural killer cell receptors. Proc Natl Acad Sci U S A. 1998 Nov 24;95(24):14326-31

Vance RE, Kraft JR, Altman JD, Jensen PE, Raulet DH. Mouse CD94/NKG2A is a natural killer cell receptor for the nonclassical major histocompatibility complex (MHC) class I molecule Qa-1(b). J Exp Med. 1998 Nov 16;188(10):1841-8

Winter CC, Gumperz JE, Parham P, Long EO, Wagtmann N. Direct binding and functional transfer of NK cell inhibitory receptors reveal novel patterns of HLA-C allotype recognition. J Immunol. 1998 Jul 15;161(2):571-7

Adams EJ, Thomson G, Parham P. Evidence for an HLA-C-like locus in the orangutan Pongo pygmaeus. Immunogenetics. 1999 Sep;49(10):865-71

Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu Rev Immunol. 1999;17:189-220

Vitale M, Castriconi R, Parolini S, Pende D, Hsu ML, Moretta L, Cosman D, Moretta A. The leukocyte Ig-like receptor (LIR)-1 for the cytomegalovirus UL18 protein displays a broad specificity for different HLA class I alleles: analysis of LIR-1 + NK cell clones. Int Immunol. 1999 Jan;11(1):29-35

Wende H, Colonna M, Ziegler A, Volz A. Organization of the leukocyte receptor cluster (LRC) on human chromosome 19q13.4. Mamm Genome. 1999 Feb;10(2):154-60

Witt CS, Dewing C, Sayer DC, Uhrberg M, Parham P, Christiansen FT. Population frequencies and putative haplotypes of the killer cell immunoglobulin-like receptor sequences and evidence for recombination. Transplantation. 1999 Dec 15;68(11):1784-9

Boyington JC, Motyka SA, Schuck P, Brooks AG, Sun PD. Crystal structure of an NK cell immunoglobulin-like receptor in complex with its class I MHC ligand. Nature. 2000 Jun 1;405(6786):537-43

Crum KA, Logue SE, Curran MD, Middleton D. Development of a PCR-SSOP approach capable of defining the natural killer

cell inhibitory receptor (KIR) gene sequence repertoires. Tissue Antigens. 2000 Oct;56(4):313-26

Khakoo SI, Rajalingam R, Shum BP, Weidenbach K, Flodin L, Muir DG, Canavez F, Cooper SL, Valiante NM, Lanier LL, Parham P. Rapid evolution of NK cell receptor systems demonstrated by comparison of chimpanzees and humans. Immunity. 2000 Jun;12(6):687-98

Martin AM, Freitas EM, Witt CS, Christiansen FT. The genomic organization and evolution of the natural killer immunoglobulin-like receptor (KIR) gene cluster. Immunogenetics. 2000 Apr;51(4-5):268-80

Wilson MJ, Torkar M, Haude A, Milne S, Jones T, Sheer D, Beck S, Trowsdale J. Plasticity in the organization and sequences of human KIR/ILT gene families. Proc Natl Acad Sci U S A. 2000 Apr 25;97(9):4778-83

Fan QR, Long EO, Wiley DC. Crystal structure of the human natural killer cell inhibitory receptor KIR2DL1-HLA-Cw4 complex. Nat Immunol. 2001 May;2(5):452-60

Gardiner CM, Guethlein LA, Shilling HG, Pando M, Carr WH, Rajalingam R, Vilches C, Parham P. Different NK cell surface phenotypes defined by the DX9 antibody are due to KIR3DL1 gene polymorphism. J Immunol. 2001 Mar 1;166(5):2992-3001

Norman PJ, Stephens HA, Verity DH, Chandanayingyong D, Vaughan RW. Distribution of natural killer cell immunoglobulin-like receptor sequences in three ethnic groups. Immunogenetics. 2001;52(3-4):195-205

Rajalingam R, Gardiner CM, Canavez F, Vilches C, Parham P. Identification of seventeen novel KIR variants: fourteen of them from two non-Caucasian donors. Tissue Antigens. 2001 Jan;57(1):22-31

Toneva M, Lepage V, Lafay G, Dulphy N, Busson M, Lester S, Vu-Trien A, Michaylova A, Naumova E, McCluskey J, Charron D. Genomic diversity of natural killer cell receptor genes in three populations. Tissue Antigens. 2001 Apr;57(4):358-62

Hsu KC, Chida S, Geraghty DE, Dupont B. The killer cell immunoglobulin-like receptor (KIR) genomic region: gene-order, haplotypes and allelic polymorphism. Immunol Rev. 2002 Dec;190:40-52

Hsu KC, Liu XR, Selvakumar A, Mickelson E, O'Reilly RJ, Dupont B. 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. 2002 Nov 1;169(9):5118-29

Khakoo SI, Geller R, Shin S, Jenkins JA, Parham P. The D0 domain of KIR3D acts as a major histocompatibility complex class I binding enhancer. J Exp Med. 2002 Oct 7;196(7):911-21

Martin MP, Gao X, Lee JH, Nelson GW, Detels R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, Trowsdale J, Wilson M, O'Brien SJ, Carrington M. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nat Genet. 2002 Aug;31(4):429-34

Maxwell LD, Wallace A, Middleton D, Curran MD. A common KIR2DS4 deletion variant in the human that predicts a soluble KIR molecule analogous to the KIR1D molecule observed in the rhesus monkey. Tissue Antigens. 2002 Sep;60(3):254-8

Moffett-King A. Natural killer cells and pregnancy. Nat Rev Immunol. 2002 Sep;2(9):656-63

Norman PJ, Carrington CV, Byng M, Maxwell LD, Curran MD, Stephens HA, Chandanayingyong D, Verity DH, Hameed K, Ramdath DD, Vaughan RW. Natural killer cell immunoglobulin-like receptor (KIR) locus profiles in African and South Asian populations. Genes Immun. 2002 Apr;3(2):86-95

Shilling HG, Guethlein LA, Cheng NW, Gardiner CM, Rodriguez R, Tyan D, Parham P. Allelic polymorphism synergizes with variable gene content to individualize human KIR genotype. J Immunol. 2002 Mar 1;168(5):2307-15

Shum BP, Flodin LR, Muir DG, Rajalingam R, Khakoo SI, Cleland S, Guethlein LA, Uhrberg M, Parham P. Conservation and variation in human and common chimpanzee CD94 and NKG2 genes. J Immunol. 2002 Jan 1;168(1):240-52

Uhrberg M, Parham P, Wernet P. Definition of gene content for nine common group B haplotypes of the Caucasoid population: KIR haplotypes contain between seven and eleven KIR genes. Immunogenetics. 2002 Jul;54(4):221-9

Vilches C, Parham P. KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. Annu Rev Immunol. 2002;20:217-51

Yawata M, Yawata N, Abi-Rached L, Parham P. Variation within the human killer cell immunoglobulin-like receptor (KIR) gene family. Crit Rev Immunol. 2002;22(5-6):463-82

Yawata M, Yawata N, McQueen KL, Cheng NW, Guethlein LA, Rajalingam R, Shilling HG, Parham P. Predominance of group A KIR haplotypes in Japanese associated with diverse NK cell repertoires of KIR expression. Immunogenetics. 2002 Nov;54(8):543-50

Martin MP, Bashirova A, Traherne J, Trowsdale J, Carrington M. Cutting edge: expansion of the KIR locus by unequal crossing over. J Immunol. 2003 Sep 1;171(5):2192-5

Pando MJ, Gardiner CM, Gleimer M, McQueen KL, Parham P. The protein made from a common allele of KIR3DL1 (3DL1*004) is poorly expressed at cell surfaces due to substitution at positions 86 in Ig domain 0 and 182 in Ig domain 1. J Immunol. 2003 Dec 15;171(12):6640-9

Carrington M, Cullen M. Justified chauvinism: advances in defining meiotic recombination through sperm typing. Trends Genet. 2004 Apr;20(4):196-205

Hansasuta P, Dong T, Thananchai H, Weekes M, Willberg C, Aldemir H, Rowland-Jones S, Braud VM. Recognition of HLA-A3 and HLA-A11 by KIR3DL2 is peptide-specific. Eur J Immunol. 2004 Jun;34(6):1673-9

Hiby SE, Walker JJ, O'shaughnessy KM, Redman CW, Carrington M, Trowsdale J, Moffett A. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med. 2004 Oct 18;200(8):957-65

Khakoo SI, Thio CL, Martin MP, Brooks CR, Gao X, Astemborski J, Cheng J, Goedert JJ, Vlahov D, Hilgartner M, Cox S, Little AM, Alexander GJ, Cramp ME, O'Brien SJ, Rosenberg WM, Thomas DL, Carrington M. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science. 2004 Aug 6;305(5685):872-4

Jiang K, Zhu FM, Lv QF, Yan LX. Distribution of killer cell immunoglobulin-like receptor genes in the Chinese Han population. Tissue Antigens. 2005 Jun;65(6):556-63

Kelley J, Walter L, Trowsdale J. Comparative genomics of natural killer cell receptor gene clusters. PLoS Genet. 2005 Aug;1(2):129-39

Kikuchi-Maki A, Catina TL, Campbell KS. Cutting edge: KIR2DL4 transduces signals into human NK cells through association with the Fc receptor gamma protein. J Immunol. 2005 Apr 1;174(7):3859-63

Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song YJ, Yang L, French AR, Sunwoo JB, Lemieux S, Hansen TH, Yokoyama WM. Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature. 2005 Aug 4;436(7051):709-13

Kirwan SE, Burshtyn DN. Killer cell Ig-like receptor-dependent signaling by Ig-like transcript 2 (ILT2/CD85j/LILRB1/LIR-1). J Immunol. 2005 Oct 15;175(8):5006-15

Stewart CA, Laugier-Anfossi F, Vély F, Saulquin X, Riedmuller J, Tisserant A, Gauthier L, Romagné F, Ferracci G, Arosa FA, Moretta A, Sun PD, Ugolini S, Vivier E. Recognition of peptide-MHC class I complexes by activating killer immunoglobulin-like receptors. Proc Natl Acad Sci U S A. 2005 Sep 13;102(37):13224-9

Whang DH, Park H, Yoon JA, Park MH. Haplotype analysis of killer cell immunoglobulin-like receptor genes in 77 Korean families. Hum Immunol. 2005 Feb;66(2):146-54

Bashirova AA, Martin MP, McVicar DW, Carrington M. The killer immunoglobulin-like receptor gene cluster: tuning the genome for defense. Annu Rev Genomics Hum Genet. 2006;7:277-300

MacFarlane AW 4th, Campbell KS. Signal transduction in natural killer cells. Curr Top Microbiol Immunol. 2006;298:23-57

Rajagopalan S, Bryceson YT, Kuppusamy SP, Geraghty DE, van der Meer A, Joosten I, Long EO. Activation of NK cells by an endocytosed receptor for soluble HLA-G. PLoS Biol. 2006 Jan;4(1):e9

Sambrook JG, Bashirova A, Andersen H, Piatak M, Vernikos GS, Coggill P, Lifson JD, Carrington M, Beck S. Identification of the ancestral killer immunoglobulin-like receptor gene in primates. BMC Genomics. 2006 Aug 15;7:209

VandenBussche CJ, Dakshanamurthy S, Posch PE, Hurley CK. A single polymorphism disrupts the killer Ig-like receptor 2DL2/2DL3 D1 domain. J Immunol. 2006 Oct 15;177(8):5347-57

Yawata M, Yawata N, Draghi M, Little AM, Partheniou F, Parham P. Roles for HLA and KIR polymorphisms in natural killer cell repertoire selection and modulation of effector function. J Exp Med. 2006 Mar 20;203(3):633-45

Guethlein LA, Abi-Rached L, Hammond JA, Parham P. The expanded cattle KIR genes are orthologous to the conserved single-copy KIR3DX1 gene of primates. Immunogenetics. 2007 Jun;59(6):517-22

Kollnberger S, Chan A, Sun MY, Chen LY, Wright C, di Gleria K, McMichael A, Bowness P. Interaction of HLA-B27 homodimers with KIR3DL1 and KIR3DL2, unlike HLA-B27 heterotrimers, is independent of the sequence of bound peptide. Eur J Immunol. 2007 May;37(5):1313-22

Martin MP, Qi Y, Gao X, Yamada E, Martin JN, Pereyra F, Colombo S, Brown EE, Shupert WL, Phair J, Goedert JJ, Buchbinder S, Kirk GD, Telenti A, Connors M, O'Brien SJ, Walker BD, Parham P, Deeks SG, McVicar DW, Carrington M. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. Nat Genet. 2007 Jun;39(6):733-40

Single RM, Martin MP, Gao X, Meyer D, Yeager M, Kidd JR, Kidd KK, Carrington M. Global diversity and evidence for coevolution of KIR and HLA. Nat Genet. 2007 Sep;39(9):1114-9

Long EO. Negative signaling by inhibitory receptors: the NK cell paradigm. Immunol Rev. 2008 Aug;224:70-84

Martin MP, Single RM, Wilson MJ, Trowsdale J, Carrington M. KIR haplotypes defined by segregation analysis in 59 Centre d'Etude Polymorphisme Humain (CEPH) families. Immunogenetics. 2008 Dec;60(12):767-74

Moesta AK, Norman PJ, Yawata M, Yawata N, Gleimer M, Parham P. Synergistic polymorphism at two positions distal to the ligand-binding site makes KIR2DL2 a stronger receptor for HLA-C than KIR2DL3. J Immunol. 2008 Mar 15;180(6):3969-79

Romero V, Azocar J, Zúñiga J, Clavijo OP, Terreros D, Gu X, Husain Z, Chung RT, Amos C, Yunis EJ. Interaction of NK inhibitory receptor genes with HLA-C and MHC class II alleles in Hepatitis C virus infection outcome. Mol Immunol. 2008 May;45(9):2429-36

Yawata M, Yawata N, Draghi M, Partheniou F, Little AM, Parham P. MHC class I-specific inhibitory receptors and their ligands structure diverse human NK-cell repertoires toward a balance of missing self-response. Blood. 2008 Sep 15;112(6):2369-80

Averdam A, Petersen B, Rosner C, Neff J, Roos C, Eberle M, Aujard F, Münch C, Schempp W, Carrington M, Shiina T, Inoko H, Knaust F, Coggill P, Sehra H, Beck S, Abi-Rached L, Reinhardt R, Walter L. A novel system of polymorphic and diverse NK cell receptors in primates. PLoS Genet. 2009 Oct;5(10):e1000688

Cadavid LF, Lun CM. Lineage-specific diversification of killer cell Ig-like receptors in the owl monkey, a New World primate. Immunogenetics. 2009 Jan;61(1):27-41

Gendzekhadze K, Norman PJ, Abi-Rached L, Graef T, Moesta AK, Layrisse Z, Parham P. Co-evolution of KIR2DL3 with HLA-C in a human population retaining minimal essential diversity of KIR and HLA class I ligands. Proc Natl Acad Sci U S A. 2009 Nov 3;106(44):18692-7

Graef T, Moesta AK, Norman PJ, Abi-Rached L, Vago L, Older Aguilar AM, Gleimer M, Hammond JA, Guethlein LA, Bushnell DA, Robinson PJ, Parham P. KIR2DS4 is a product of gene conversion with KIR3DL2 that introduced specificity for HLA-A*11 while diminishing avidity for HLA-C. J Exp Med. 2009 Oct 26;206(11):2557-72

Hammond JA, Guethlein LA, Abi-Rached L, Moesta AK, Parham P. Evolution and survival of marine carnivores did not require a diversity of killer cell Ig-like receptors or Ly49 NK cell receptors. J Immunol. 2009 Mar 15;182(6):3618-27

Norman PJ, Abi-Rached L, Gendzekhadze K, Hammond JA, Moesta AK, Sharma D, Graef T, McQueen KL, Guethlein LA, Carrington CV, Chandanayingyong D, Chang YH, Crespí C, Saruhan-Direskeneli G, Hameed K, Kamkamidze G, Koram KA, Layrisse Z, Matamoros N, Milà J, Park MH, Pitchappan RM, Ramdath DD, Shiau MY, Stephens HA, Struik S, Tyan D, Verity DH, Vaughan RW, Davis RW, Fraser PA, Riley EM, Ronaghi M, Parham P. Meiotic recombination generates rich diversity in NK cell receptor genes, alleles, and haplotypes. Genome Res. 2009 May;19(5):757-69

Pende D, Marcenaro S, Falco M, Martini S, Bernardo ME, Montagna D, Romeo E, Cognet C, Martinetti M, Maccario R, Mingari MC, Vivier E, Moretta L, Locatelli F, Moretta A. Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR and redefinition of inhibitory KIR specificity. Blood. 2009 Mar 26;113(13):3119-29

Purdy AK, Campbell KS. Natural killer cells and cancer: regulation by the killer cell Ig-like receptors (KIR). Cancer Biol Ther. 2009 Dec;8(23):2211-20

VandenBussche CJ, Mulrooney TJ, Frazier WR, Dakshanamurthy S, Hurley CK. Dramatically reduced surface expression of NK cell receptor KIR2DS3 is attributed to multiple residues throughout the molecule. Genes Immun. 2009 Mar;10(2):162-73

Abi-Rached L, Kuhl H, Roos C, ten Hallers B, Zhu B, Carbone L, de Jong PJ, Mootnick AR, Knaust F, Reinhardt R, Parham P, Walter L. A small, variable, and irregular killer cell Ig-like

receptor locus accompanies the absence of MHC-C and MHC-G in gibbons. J Immunol. 2010 Feb 1;184(3):1379-91

Abi-Rached L, Moesta AK, Rajalingam R, Guethlein LA, Parham P. Human-specific evolution and adaptation led to major qualitative differences in the variable receptors of human and chimpanzee natural killer cells. PLoS Genet. 2010 Nov 4;6(11):e1001192

Alter G, Jost S, Rihn S, Reyor LL, Nolan BE, Ghebremichael M, Bosch R, Altfeld M, Lauer GM. Reduced frequencies of NKp30+NKp46+, CD161+, and NKG2D+ NK cells in acute HCV infection may predict viral clearance. J Hepatol. 2011 Aug;55(2):278-88

Davidson CL, Li NL, Burshtyn DN. LILRB1 polymorphism and surface phenotypes of natural killer cells. Hum Immunol. 2010 Oct;71(10):942-9

Fadda L, Borhis G, Ahmed P, Cheent K, Pageon SV, Cazaly A, Stathopoulos S, Middleton D, Mulder A, Claas FH, Elliott T, Davis DM, Purbhoo MA, Khakoo SI. Peptide antagonism as a mechanism for NK cell activation. Proc Natl Acad Sci U S A. 2010 Jun 1;107(22):10160-5

Hiby SE, Apps R, Sharkey AM, Farrell LE, Gardner L, Mulder A, Claas FH, Walker JJ, Redman CW, Morgan L, Tower C, Regan L, Moore GE, Carrington M, Moffett A. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. J Clin Invest. 2010 Nov 1;120(11):4102-10

Knapp S, Warshow U, Hegazy D, Brackenbury L, Guha IN, Fowell A, Little AM, Alexander GJ, Rosenberg WM, Cramp ME, Khakoo SI. Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. Hepatology. 2010 Apr;51(4):1168-75

Orr MT, Murphy WJ, Lanier LL. 'Unlicensed' natural killer cells dominate the response to cytomegalovirus infection. Nat Immunol. 2010 Apr;11(4):321-7

Parham P, Abi-Rached L, Matevosyan L, Moesta AK, Norman PJ, Older Aguilar AM, Guethlein LA. Primate-specific regulation of natural killer cells. J Med Primatol. 2010 Aug;39(4):194-212

Pyo CW, Guethlein LA, Vu Q, Wang R, Abi-Rached L, Norman PJ, Marsh SG, Miller JS, Parham P, Geraghty DE. Different patterns of evolution in the centromeric and telomeric regions of group A and B haplotypes of the human killer cell Ig-like receptor locus. PLoS One. 2010 Dec 29;5(12):e15115

Rajagopalan S, Long EO. Antagonizing inhibition gets NK cells going. Proc Natl Acad Sci U S A. 2010 Jun 8;107(23):10333-4

Traherne JA, Martin M, Ward R, Ohashi M, Pellett F, Gladman D, Middleton D, Carrington M, Trowsdale J. Mechanisms of copy number variation and hybrid gene formation in the KIR immune gene complex. Hum Mol Genet. 2010 Mar 1;19(5):737-51

Vidal-Castiñeira JR, López-Vázquez A, Díaz-Peña R, Alonso-Arias R, Martínez-Borra J, Pérez R, Fernández-Suárez J, Melón S, Prieto J, Rodrigo L, López-Larrea C. Effect of killer immunoglobulin-like receptors in the response to combined treatment in patients with chronic hepatitis C virus infection. J Virol. 2010 Jan;84(1):475-81

Gonzalez-Galarza FF, Christmas S, Middleton D, Jones AR. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. Nucleic Acids Res. 2011 Jan;39(Database issue):D913-9

IPD KIR polymorphism database.

http://www.ebi.ac.uk/ipd/kir/stats.html

This article should be referenced as such:

Borhis G, Khakoo SI. NK cell receptors: evolution and diversity. Atlas Genet Cytogenet Oncol Haematol. 2011; 15(9):787-796.