Human-specific evolution of killer cell immunoglobulin-like receptor recognition of major histocompatibility complex class I molecules

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In placental mammals, natural killer (NK) cells are a population of lymphocytes that make unique contributions to immune defence and reproduction, functions essential for survival of individuals, populations and species. Modulating these functions are conserved and variable NK-cell receptors that recognize epitopes of major histocompatibility complex (MHC) class I molecules. In humans, for example, recognition of human leucocyte antigen (HLA)-E by the CD94:NKG2A receptor is conserved, whereas recognition of HLA-A, B and C by the killer cell immunoglobulin-like receptors (KIRs) is diversified. Competing demands of the immune and reproductive systems, and of T-cell and NK-cell immunity—combined with the segregation on different chromosomes of variable NK-cell receptors and their MHC class I ligands—drive an unusually rapid evolution that has resulted in unprecedented levels of species specificity, as first appreciated from comparison of mice and humans. Counterparts to human KIR are present only in simian primates. Observed in these species is the coevolution of KIR and the four MHC class I epitopes to which human KIR recognition is restricted. Unique to hominids is the emergence of the MHC-C locus as a supplier of specialized and superior ligands for KIR. This evolutionary trend is most highly elaborated in the chimpanzee. Unique to the human KIR locus are two groups of KIR haplotypes that are present in all human populations and subject to balancing selection. Group A KIR haplotypes resemble chimpanzee KIR haplotypes and are enriched for genes encoding KIR that bind HLA class I, whereas group B KIR haplotypes are enriched for genes encoding receptors with diminished capacity to bind HLA class I. Correlating with their balance in human populations, B haplotypes favour reproductive success, whereas A haplotypes favour successful immune defence. Evolution of the B KIR haplotypes is thus unique to the human species.

Keywords: natural killer cells; major histocompatibility complex; balancing selection

1. INTRODUCTION

From their variable cell-surface receptors, that detect infection, cancer and other physiological perturbations, lymphocytes are divided into three broad types. These comprise the B cells and T cells that use gene rearrangement and somatic mutation to diversify their variable antigen receptors (immunoglobulins and T-cell receptors (TCRs) respectively), and the natural killer (NK) cells that do not employ these mechanisms. In their place, NK cells use transcriptional regulation of a variety of receptor genes to form and maintain a diverse repertoire of NK cells with heterogeneous cell-surface phenotype [1].

NK cells exert their functional effects by physically interacting with other types of cell, engagements that can lead to the killing of cells damaged by infection or malignancy, and to the secretion of cytokines that recruit other inflammatory immune system cells [2]. NK cells contribute to innate immunity, the early phase of an immune response, when NK-cell interactions with dendritic cells can help initiate the adaptive immune response mediated by B and T cells, but only if and when it is necessary. Further distinguishing NK cells from B and T cells is their role in placental reproduction [3]. Implantation of an embryo into the uterus and formation of the placenta involves interactions between maternal uterine NK cells and foetal extra-villous trophoblast cells that cause the latter to invade the mother’s spiral arteries and convert them into large vessels capable of supplying the placenta with sufficient blood to nourish the baby to term. NK cells thus make vital contributions to the immune system and the reproductive system, the former being essential for day-to-day survival of human individuals, the latter for the generation-to-generation survival of human populations and the human species.

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In their cell-surface phenotype and function, NK cells are more like T cells than B cells, and more closely resemble the CD8-bearing killer T cells than the CD4-bearing helper T cells [1]. Central to killer T-cell biology are the interactions of αβ TCRs with small 8–10 amino acid peptides presented by major histocompatibility complex (MHC) class I molecules. In analogous fashion, NK-cell receptors for MHC class I have similar critical influences on NK-cell development and response. In a process known as education for human NK cells [4–6] and licensing for mouse NK cells [7], developmental interactions between MHC class I ligands and cognate NK-cell receptors determine how mature NK cells carrying such receptors can respond to unhealthy cells exhibiting perturbed expression of the MHC class I ligand. Likewise, the strength of NK-cell effector functions can be modulated by the strength of the avidity between allelic variants of an NK-cell receptor and its cognate MHC class I ligand [5,8]. Despite the striking parallels, there are many differences in the way that NK-cell and T-cell receptors for MHC class I guide and regulate their respective lymphocyte populations.

2. GENETIC COMPLEXES ENCODING NATURAL KILLER CELL RECEPTORS AND LIGANDS

Identified in the 1930s as highly polymorphic antigens that determine the rejection of transplanted tissues and organs, MHC class I molecules were studied for the next four decades in the non-physiological context of clinical transplantation (reviewed by Klein [9]). Although their physiological function of presenting antigens to T cells unfolded in the 1970s and 1980s, it was not until the 1990s that the important influence that MHC class I molecules exert on NK-cell biology was appreciated [10]. The human MHC is alternatively called the human leucocyte antigen (HLA) complex, a name reflecting its discovery and initial characterization using antibody-based serological assays that distinguish different antigens. The approximately 4.8 Mb HLA complex on chromosome 6 contains many immune system genes and is the most highly polymorphic segment of the human genome [11,12]. Of the six expressed HLA class I genes, HLA-A, -B, and -C are extraordinarily polymorphic, whereas HLA-E, -F and -G are conserved (figure 1). All these genes except HLA-F have been shown to encode ligands for NK-cell receptors. For decades, the function of HLA-F has been an enigma, but a recent report raises the possibility that it acts as a kind of chaperone that retrieves other HLA class I molecules that have become unfolded at the plasma membrane and escorts them inside the cell [13].

Complementing the MHC are two further genetic complexes containing families of genes that encode NK-cell receptors: the natural killer complex (NKC) on chromosome 12 [14] and the leucocyte receptor complex (LRC) on chromosome 19 (figure 1) [15,16]. The NKC encodes receptors whose ligand-binding domains have a structure related to that of calcium-dependent carbohydrate-binding proteins called lectins. But instead of binding to carbohydrates, the NK-cell receptors have evolved to bind protein ligands and some of them bind to MHC class I. Critical human NKC-encoded receptors are the heterodimeric receptors CD94:NKG2A (an inhibitory receptor) and CD94:NKG2C (an activating receptor), which both recognize complexes of HLA-E and peptides derived from the leader sequences of other HLA class I (figure 1) [17]. The functional consequence of this composite specificity is that CD94:NKG2 receptors are sensors that monitor the total amount HLA class I made by a cell and how it changes in the context of disease.
The LRC encodes receptors whose ligand-binding domains are made up from several modules each of which is an immunoglobulin-like domain. Of particular interest here is the diverse family of human killer cell immunoglobulin-like receptors (KIRs), some of which recognize the polymorphic HLA-A, -B and -C molecules. In a complementary fashion to CD94:NKG2A/C, these KIRs monitor the presence and level of individual HLA class I allotypes on cell surfaces. Consistent with these complementary functions, HLA-E and CD94:NKG2 are conserved in the human population, whereas KIR and HLA-A, -B and -C are highly diversified (figure 1) [18].

3. COUNTERPARTS TO THE HUMAN KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTOR FAMILY ARE PRESENT ONLY IN SIMIAN PRIMATES
Comparing a range of mammalian species has shown that most of them do not have a diversified family of KIR genes (figure 2). For example, the KIR locus appears deleted from dog and cat genomes; and in the mouse genome, the two KIR genes are not in the LRC but on the X chromosome [26], with only one of them being expressed by NK cells [27]. Seals have a single, conserved and functional KIR gene [19]; but in prosimians, the single KIR gene is non-functional [20]. To date, diversified families of KIR genes have been found only for simian primates (monkeys, apes and the human species) and cattle, a ruminant [20–25,28–33]. However, the primate and cattle KIR families diverged ~135 million years ago, prior to the radiation of placental mammals. At that time an ancestral KIR gene duplicated to form two daughter genes: KIR3DL and KIR3DX [34,35]. Subsequently, the KIR3DL gene exclusively expanded in the simian primates, whereas the KIR3DX gene degenerated to become a pseudogene. Conversely, the KIR3DX gene expanded in cattle (and probably related ruminant species), whereas KIR3DL remained a single-copy gene. Although cattle and simian primates both have diverse KIR gene families, they are clearly the products of independent expansions [34]. Further emphasizing the restriction of diverse KIR3DL to the simian primates, prosimian primates have expanded and diversified the CD94 and NKG2 families of NKC genes in the context of their non-functional KIR [20]. Particularly extreme in their divergence from the human situation are rodents (for example mouse and rat), who use diverse families of NKC-encoded Ly49 receptors as their variable NK-cell receptors for MHC class I [36,37]. In contrast to the flourishing Ly49 gene families of rodents, the single human Ly49 gene is non-functional [38].

4. KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS RECOGNIZE FOUR MUTUALLY EXCLUSIVE EPITOPES OF HUMAN LEUCOCYTE ANTIGEN CLASS I
HLA-E is highly selective in binding peptides derived from HLA class I leader sequences [39]. Consequently, the CD94:NKG2A/C receptors are highly peptide-specific. The interactions of KIR with HLA class I are also sensitive to the sequence of the bound peptides [40–43]. Three-dimensional structures show that the KIR-binding site on the HLA class I molecule overlaps with that of the αβ TCR, and involves the face formed by the exposed parts of the α helices of the α1 and α2 domains and of the outstretched peptide gripped between them (figure 3) [44]. Direct contact is possible...
are shown on the ribbon diagram of green lines, respectively. HLA class I residues involved in TCR binding to MHC class I are given by the red and blue; and C2, red, epitopes. Population frequencies were obtained from http://www.allelefrequencies.net [51].

Figure 3. Killer cell immunoglobulin-like receptor (KIR) and the αβ T-cell receptor (TCR) bind to overlapping sites on human leucocyte antigen (HLA) class I. The areas of KIR and TCR binding to MHC class I are given by the red and green lines, respectively. HLA class I residues involved in direct contact [44,45] are shown on the ribbon diagram of the α1 and α2 domains in red for KIR binding, green for TCR binding, and yellow for binding to both KIR and TCR. Shown are position 80, the residue that determines the C1 and C2 specificities of lineage III KIR [44,46], and position 83 that is critical for the binding of lineage II KIR to the Bw4 epitopes of HLA-A and HLA-B [41,47]. The HLA structure used to produce the ribbon diagram was PDB ID:1EFX.

with peptide residues seven and eight, and indirect effects may also arise from other peptide positions that interact with the pockets of the HLA class I binding groove [47]. Although not well studied, the peptide sensitivity of KIR binding to HLA class I appears to vary with the KIR. For example, KIR3DL2 binding to HLA-A3 and HLA-A11 appears to be very peptide-dependent, because only one peptide (derived from Epstein–Barr virus (EBV)) has been shown to be permissive for the interaction [43]. Less fastidious are the HLA-C-specific KIRs, for which around 40 per cent of the peptides that bind to HLA-C are compatible with KIR interaction [40,48–50]. That the KIR- and αβ TCR-binding sites physically overlap raises the possibility that the individual selection pressures exerted on HLA class I by T-cell and NK-cell immunity can compete with each other (figure 3). In other words, a variant HLA class I selected for its beneficial T-cell response to one infection might have detrimental consequences for a subsequent NK-cell response against another infectious agent, and vice versa.

The interaction between KIR and HLA class I is relatively rigid, involving little accommodation through conformational change [44]. Only a fraction of the HLA-A, -B and -C variants interact with KIRs and these all carry one of four mutually exclusive epitopes (A3/11, Bw4, C1 and C2) that are structural variations on a theme (figure 4). These epitopes are alternatively referred to as KIR ligands, particularly in the clinical literature pertaining to bone marrow transplantation and the role of donor-derived NK cells in improving the survival of transplanted patients [52–55]. That all HLA-C allotypes have either the C1 or C2 epitope, whereas only 45 per cent of HLA-A and 36 per cent of HLA-B allotypes are KIR ligands, is consistent with HLA-C having evolved to be a superior and more specialized ligand for KIR [56,57]. This distribution also shows how a majority of HLA-A and -B allotypes do not function as KIR ligands and are thus free to evolve exclusively under pressure from the T-cell response. HLA-C is of more recent origin than HLA-A and -B and probably evolved from an HLA-B-like ancestor that carried the C1 epitope [58]. Studies to compare the HLA class I specificities of mutant human and ape KIRs show that hominoid KIRs are inherently restricted to recognizing HLA class I allotypes carrying the A3/11, Bw4, C1 or C2 epitope, further emphasizing the partition of HLA-A and -B allotypes into those that serve as KIR ligands and those that cannot [56,57].

5. POPULATION BIOLOGY AND GENETICS OF KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS

There are 13 expressed human KIR genes and two KIR pseudogenes (figure 5). KIR2DS1, 2, 3, 4 and 5 are dedicated activating receptors, whereas KIR2DL1, 2DL2/3 and 2DL5 are dedicated inhibitory receptors. KIR2DL4 has potential for both activating and inhibitory functions, whereas KIR3DL1/S1 is unusual in having mutually exclusive subsets of allotypes with activating (KIR3DS1) and inhibitory (KIR3DL1) function [59]. Haplotypes of the KIR locus differ in their content of KIR genes [33], an important feature that is illustrated for several common KIR haplotypes in figure 5 [23]. Three conserved genes (KIR3DL3, 2DL4 and 3DL2) form the common framework that defines two regions of gene-content diversity, one in the centromeric part of the locus and the other in the telomeric part [60].

Only five of the 13 human KIRs have been demonstrated to recognize HLA class I: A3/11 by KIR3DL2 [61], Bw4 by KIR3DL1 (but not KIR3DS1) [62,63], C2 by KIR2DL1 and 2DS1 [64], C1 and some C2 by KIR2DL2/3 [46,65], a mix of some C1, some C2 and A11 by KIR2DS4 [66] and HLA-G by KIR2DL4 [67] (table 1). In contrast, KIR2DS2, 2DS3, 2DS5, 2DL5, 3DS1 and 3DL3 remain orphan receptors for which no ligand has yet been identified. In the case of KIR2DS2, it is likely that at one time it did bind to...
Figure 5. Killer cell immunoglobulin-like receptor (KIR) haplotypes vary in both gene content and allelic diversity. Shown are the gene and allele content of 27 KIR haplotypes for which complete sequences have been determined [23]. Haplotypes are grouped by gene content (A or B haplotypes) and then further subdivided by their centromeric (Cen) and telomeric (Tel) gene-content motifs. Framework genes are shaded in grey, gene-content motifs. Framework genes are shaded in grey, A haplotype characteristic genes/alleles in red and B haplotype characteristic genes/alleles in blue. Partial sequences are indicated by stippling and ‘part’ indicates where allelic identity was not fully determined. ‘Typing’ indicates that the KIR gene was determined to be present by genotyping.

Table 1. Human leukocyte antigen epitopes recognized by killer cell immunoglobulin-like receptor.

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HLA class I but was then actively selected to lose that function [68,69]. Population studies provide an alternative approach for assessing the functional benefit of the enigmatic orphan KIR. To date, approximately 200 populations have been studied for KIR gene content (http://www.alllelefrequencies.net [51]). With the exception of KIR2DS3 and KIR2DL5B, which are absent from some Amerindian tribes [70,71], all populations have significant frequencies for all the KIR genes. Likewise, all populations have both inhibitory KIR3DL1 that binds to Bw4 [62] and activating KIR3DS1 that does not bind Bw4 or other HLA class I [63]. Such retention, particularly in the case of Amerindian populations who have experienced successive population bottlenecks and severe epidemics of infectious disease, is unlikely to have occurred by chance and argues that the orphan KIRs serve useful functions, but this need not necessarily involve interaction with HLA class I. A precedent is set by KIR3DL2, which in addition to recognizing the A3/11 epitope of HLA class I [61] also recognizes microbial products and carries them inside cells for possible delivery to Toll-like receptors [72,73]. That loss of KIR2DS3 and KIR2DL5B has been tolerated by some populations could reflect the sequence similarities of these KIRs with KIR2DS5.
and KIR2DL5A, respectively. For KIR2DS3, its poor folding in the endoplasmic reticulum and inability to reach the NK cell surface could also be a factor [74].

On the basis of KIR gene content, two groups of KIR haplotype have been defined. This concept is well illustrated by the Yucpa population of Amerindians who have only two major KIR gene-content haplotypes, one of group A and one of group B, which are present at roughly equal frequencies (figure 6). Differences of gene content are seen in both the centromeric and telomeric regions; and at the allele level, the two haplotypes have no KIR factor in common [75]. The group A haplotype has a content of seven genes of which six encode KIR that bind HLA class I and KIR2DL1 allele of the 003 motif. In disease-association studies, the effects of the B motifs appear dominant as is consistent with them having loss of function [78].

6. MAJOR DIFFERENCES IN HUMAN AND CHIMPANZEE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS

Comparing the KIR locus in different species of simian primate shows an extraordinary degree of species specificity that attests to the rapid and variable evolution of KIR (figure 2). Phylogenetic analysis of the nucleotide sequences encoding simian primate KIR shows they form four discrete lineages that have coevolved with their target epitopes [21]. Presence in Old World monkeys of multiple HLA-A- and -B-like loci is associated with an expansion of lineage II KIR related to the human lineage II KIR3DL1 and 3DL2 that recognize the Bw4 and A3/11 epitopes, respectively. Likewise, the emergence of an HLA-C orthologue in orangutans is associated with expansion of lineage III KIR related to the human lineage III KIR2DL1, 2DS1 and 2DL2/3 that recognize HLA-C.

As the chimpanzee is the living species most closely related to humans, we have extensively studied the function and population biology of chimpanzee KIR, so as to provide a valid assessment of what features of the human system are shared with other species and what features are unique (figure 7).

Although both humans and chimpanzees have 13 KIR genes, only 3DL3, 2DL4, 2DL5 and 2DS4 are orthologous [30]. The framework of the KIR locus in the two species is similar but the distribution of genes within this framework is qualitatively different (figure 8). Whereas the variable gene content in the human KIR locus is evenly distributed between the centromeric and telomeric regions, all 10 chimpanzee KIR genes that contribute to variable gene content are packed together in the centromeric region. This leaves the telomeric region empty except for the 3DL1/2 lineage II framework gene which encodes a receptor having a specificity for MHC-A and MHC-B that combines vsa [23,77]. The convention has been to describe all such recombinant haplotypes as B haplotypes, reserving the A haplotype designation for haplotypes that have both a centromeric and a telomeric A motif. In disease-association studies, the effects of the B motifs appear dominant as is consistent with them having loss of function [78].

![Figure 6. Group A and B haplotypes are present at very even frequencies in the Yucpa Amerindians. The structures of the two Yucpa KIR gene-content haplotypes are shown [70,75]. Genes are coloured according to the binding specificity of the encoded receptor. Green denotes KIRs that bind HLA class I. Yellow denotes KIRs that do not bind HLA class I. Grey denotes KIR for which ligands are unknown. White denotes pseudogenes. Dots indicate absence of a gene. The KIR locus is situated at chromosome 19q13.4; its centromeric boundary corresponds to 0 kb in the horizontal scale and its telomeric end to 230 kb.](http://rstb.royalsocietypublishing.org/)
elements of the Bw4 and A3/11 specificities of human lineage II KIR3DL1 and 3DL2, respectively [80]. All nine of the chimpanzee lineage III bind HLA class I, compared with only three of six human lineage III [58,69]. In addition to an orthologue of human 2DS4, the chimpanzee has a battery of three C1-specific KIRs (one activating and two inhibitory) and five C2-specific KIRs (one activating and four inhibitory) that vary in both signalling and ligand-binding domains, and display more allelic variability than their human counterparts.

Figure 7. Coevolution of KIR with cognate MHC class I ligands. In the columns corresponding to E, A, B, C and G, coloured boxes indicate the presence in other primate species of one or more counterparts to the corresponding human HLA class I isotype. The cognate NK-cell receptor for each HLA class I is shown at the bottom of the column. In the column under ‘KIR’, characteristic features of the KIR in each non-human primate species are given. Bw4/Bw6 and C1/C2 are pairs of mutually exclusive epitopes at HLA-B and HLA-C, respectively.

Figure 8. Variation in the chimpanzee KIR locus is restricted to the centromeric interval. This diagram compares the organization and gene-content variability of the chimpanzee and human KIR loci. The branching pathways represent different gene-content motifs and they are combined to produce different KIR haplotypes. Framework genes are coloured grey; chimpanzee-specific lineage III KIR specific for the C1 and C2 epitopes of HLA-C, green; genes characteristic of human A haplotype, red; genes characteristic of human B haplotypes, blue; 2DP1 and 2DL1 in humans have been coloured grey indicating their presence both on A and B haplotypes. Adapted from Abi-Rached et al. [79]. C1 or C2 in a gene box denotes the receptor’s epitope specificity.

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Importantly, however, the chimpanzee KIR haplotypes do not divide into two groups as is the case for the human KIR haplotypes.

7. AN EVOLUTIONARY COMPROMISE FOR HUMAN KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS THAT WAS NOT MADE BY CHIMPANZEE KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS

In the context of hominoid evolution, during which HLA-C evolved specifically as a KIR ligand and the C1 epitope preceded the C2 epitope by several million years, the chimpanzee KIR locus has taken this progression to a higher level than the human KIR locus. The majority of chimpanzee KIRs are HLA-C receptors and the C2-specific receptors outweigh the C1-specific receptors in number. In contrast, the human system represents a less robust or compromised system in which the group A KIR haplotypes are more similar to the chimpanzee KIR haplotypes, whereas the group B KIR haplotypes have accumulated genes encoding KIRs with reduced or no binding to HLA class I.

Common disorders of reproduction, such as pre-eclampsia, spontaneous abortion and foetal growth restriction, have been associated with pregnancies in which the mother is homozygous for group A KIR haplotypes and the foetus has HLA-C bearing the C2 epitope [81,82]. This combination implicates interactions between foetal C2 and maternal inhibitory C2-specific KIR2DL1 in the disease-causing mechanism. Consistent with this model, activating C2-specific KIR2DS1 is a protective factor on maternal B KIR haplotypes [83]. Indicating that these pregnancy disorders have been a major selective force on human populations is the observed inverse correlation between the frequencies of C2 bearing HLA-C and group A KIR haplotypes (figure 9). This correlation strongly argues that pressure from human reproduction drove the evolution of the group B KIR haplotypes.

The common disorders of pregnancy are associated with insufficient invasion of the uterus by foetal extravillous trophoblast cells, which enlarge maternal blood vessels called spiral arteries so that they will be capable of supplying the growing baby with sufficient nutrition [3]. This remodelling function of the trophoblast appears to be guided through physical and chemical interactions with specialized uterine NK cells of the mother, which have phenotypic and functional properties that are different from those of the majority of blood NK cells [84]. Extra-villous trophoblast uniquely expresses an abundance of HLA-C but not HLA-A and -B [85]. Thus, the underlying disease-causing mechanism probably involves interaction between C2-bearing HLA-C on the foetal trophoblast and KIR2DL1 on the maternal uterine NK cells. That this type of interaction has been attenuated in humans, by evolution of the group B KIR haplotypes, but not in chimpanzees indicates a selective pressure that demanded an ever-increasing supply of maternal blood to feed the foetus. An important difference that distinguishes human and chimpanzee evolution, since they last shared a common ancestor more than 6 Myr ago, is that the adult human brain is now more than three times the size of an adult chimpanzee brain [86]. The evolution of ever-bigger brains would have been energetically expensive, necessitating continual improvement of the supply of maternal blood to the placenta. This improvement seems to have been accomplished by the evolution of the KIR B haplotypes that have an activating C2-specific KIR that counters the effect of inhibitory KIR2DL1, and a
series of inhibitory KIRs, including allotypes of KIR2DL1 [76], that have been selected for attenuation or loss of function [23].

NK cells have been strongly implicated in providing immunity against viral infections [87]. For example, a person lacking NK cells was susceptible to fulminating immunity against viral infections [87]. For example, a person lacking NK cells was susceptible to fulminating immunity against viral infections [87].

This difference may in part explain why chimpanzees are relatively resistant to a variety of infections that plague the modern human population [91].

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