PERSPECTIVES

OPINION

Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution

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Abstract | Natural killer (NK) cells have roles in immunity and reproduction that are controlled by variable receptors that recognize MHC class I molecules. The variable NK cell receptors found in humans are specific to simian primates, in which they have progressively co-evolved with MHC class I molecules. The emergence of the *MHC-C* gene in hominids drove the evolution of a system of NK cell receptors for MHC-C molecules that is most elaborate in chimpanzees. By contrast, the human system of MHC-C receptors seems to have been subject to different selection pressures that have acted in competition on the immunological and reproductive functions of MHC class I molecules. We suggest that this compromise facilitated the development of the bigger brains that enabled archaic and modern humans to migrate out of Africa and populate other continents.

Comparisons of mouse and human genomes have shown that the biggest differences — in terms of both gene content and gene sequence — occur in genes of the immune and reproductive systems[1,2]. This variability reflects the vital importance of these two systems and of their genetic diversity in mammalian populations. Working at the interface of immune defence and reproduction are natural killer (NK) cells, which contribute to innate immunity, adaptive immunity and placentation. Modulating these functions are variable NK cell receptors that recognize polymorphic MHC class I molecules. Because of the competing and changing requirements for their various functions, these receptor–ligand systems evolve rapidly and are inherently unstable. As we discuss, in the course of human history the acquisition of bigger brains and upright walking put limitations on immunity and reproduction, but enabled humans to expand their geographic range out of Africa to other continents. The success of these migrations probably required the maintenance of a minimal level of diversity in both polymorphic MHC class I molecules and variable NK cell receptors. Loss of diversity, as occurs in population bottlenecks, could be compensated for by the selection of new variants or by the adaptive introgression of old variants from archaic humans into modern human populations.

Convergence of lymphocyte receptors

All vertebrate and invertebrate animals have an innate immune system, but adaptive immunity is thought to be a uniquely vertebrate feature[3]. Underlying adaptive immunity are variable, clonally distributed lymphocyte receptors that are the products of rearranged genes. Such systems have evolved independently in jawed and jawless vertebrates. Almost all extant vertebrates are jawed and have variable B and T cell receptors built from immunoglobulin-like domains. In jawless vertebrates — the lampreys and hagfish — lymphocytes resembling B and T cells have variable receptors constructed from leucine-rich repeats[4]. Although they are structurally unrelated, the variable B and T cell receptors of jawed and jawless vertebrates have remarkably parallel functions, which are probably the consequence of convergent evolution driven by the universal selection pressures imposed by pathogens.

More prone to convergent evolution are the variable receptors of NK cells, which are lymphocytes that contribute to both innate and adaptive immunity and also, in placental mammals, to reproduction[5,6]. Whereas the convergence of B and T cell receptors is seen only between species that diverged more than 500 million years ago, the convergence of variable NK cell receptors is apparent among placental mammals that diverged 55–65 million years ago[7]. The receptors in question recognize polymorphic determinants of MHC class I molecules and are the products of diverse families of non-rearranging genes that exhibit allelic polymorphism and gene-content variability[8–10]. During development, NK cells are 'educated' by self MHC class I molecules to enable them to monitor other cells for the quality and quantity of their MHC class I expression[11]. Changes in MHC class I expression can be a sign of infection, cancer or invading cells from another person, as occurs naturally in pregnancy[5]. Although we focus here on the variable interactions between NK cell receptors and MHC class I molecules, we must emphasize that this diversifying element to NK cell function occurs always in the context of conserved interactions between other NK cell receptors and their MHC class I ligands, such as that between human CD94–NKG2A and HLA-E[12].

Variable NK cell receptors are unstable

The variable NK cell receptors of mice and humans, the species most studied by immunologists, are the products of convergent evolution. Whereas immunoglobulin-like domains form the MHC class I-binding sites of human killer cell immunoglobulin-like receptors (KIRs), the binding sites of mouse LY49 family receptors are formed from a different type of domain, which resembles that found in calcium-dependent lectins[13]. Emphasizing their independent evolution, KIRs and LY49 receptors bind to non-overlapping sites on the surface of MHC class I molecules[9] (FIG. 1a). Exploratory phylogenetic comparisons have identified a few other species that use LY49 receptors (namely rats and horses) or KIRs (namely simian primates and cattle) as variable NK cell receptors[10]. No species is known to diversify both KIRs and LY49 receptors, but several species diversify neither, preserving *KIR* and *LY49* as conserved, single-copy genes[14].

Although they are superficially similar, the cattle and simian-primate KIR families are divergent, having arisen from different founder genes: *KIR3DX* and *KIR3DL*, respectively[15]. These genes arose through the duplication of an ancestral KIR gene in a non-placental mammal ~140 million years ago, and both genes were inherited by placental mammals. In cattle, *KIR3DX* was duplicated and diversified[16], whereas *KIR3DL* became non-functional. The converse occurred in simian primates, in which *KIR3DL* diversified and *KIR3DX* became inactive. Prosimian primates lack *KIR3DL*, have single copies of *KIR3DX* and *LY49*, and instead have diversified CD94 and NKG2 genes[17], which in humans encode the conserved CD94–NKG2 receptors for HLA-E[18] (FIG. 1b). The independent evolution of four families of variable NK cell receptors has been revealed by the study of less than 1% of the more than 4,000 extant species of placental mammal[19], indicating that this phenomenon might have occurred many times during the 132-million-year history of these animals[7].

Implicit to the generation of a new family of variable NK cell receptors is the collapse of an older family, which occurs because the functions of the older family are either lost or no longer useful. Several features of the mouse and human systems of variable NK cell receptors and MHC class I ligands make them vulnerable to such an end. First, because the receptors and their MHC class I ligands are variable and segregate on different chromosomes, in any generation only a fraction of individuals has any given ligand–receptor interaction[20]. In a population bottleneck with accompanying genetic drift, either a ligand or its cognate receptor could be lost from the population, and successive population bottlenecks could have the cumulative effect of eliminating all functional ligand–receptor interactions. Second, polymorphic MHC class I molecules that are ligands for variable NK cell receptors also present antigens to $CD8^+$ T cells, which creates competition between NK cell- and T cell-mediated immunity. Thus, during epidemics of infectious disease, the combination of decreasing population size, genetic drift and selection for those MHC class I variants that induce superior T cell immune responses could have the 'unintended' consequence of eliminating other MHC class I variants that are NK cell receptor ligands. Third, a similar form of competition could occur between NK cell functions in immunity and reproduction. An episode of selection that exerts pressure on one of these systems could eliminate ligand–receptor interactions that are useful to the other system (see below).

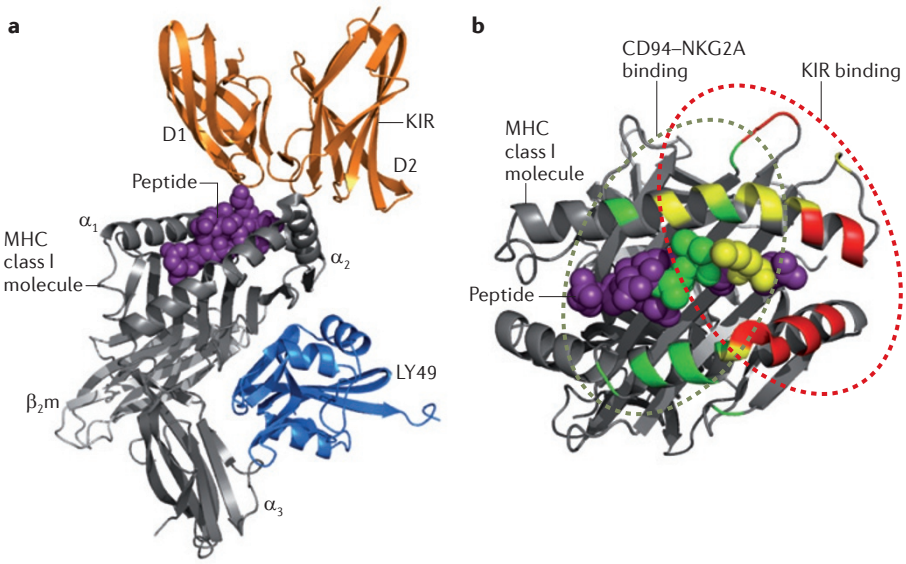


Figure 1 | **Convergent evolution of variable NK cell receptors for MHC class I. a** | This panel shows how human killer cell immunoglobulin-like receptors (KIRs) and mouse LY49 lectin-like receptors bind to different and non-overlapping sites on the surface of MHC class I molecules. KIRs interact with the upward face of the MHC class I molecule formed by the helices of the α_1 and α_2 domains and the peptide bound in the groove between them[100]. By contrast, LY49 receptors bind underneath the peptide-binding groove and interact with all four domains of the MHC class I molecule: α_1, α_2, α_3 and β_2-microglobulin (β_2m)[9]. **b** | This panel shows how human KIRs and the human lectin-like receptor CD94–NKG2A bind to overlapping sites on the surface of MHC class I molecules. The ribbon diagram shows the upward face of the MHC class I molecule with the space-filling image of the peptide between the helices of the α_1 and α_2 domains. The dashed ellipses and colouring of the ribbon diagram denote the areas that are bound by KIRs (red) and CD94–NKG2A (green). The overlap of the binding sites is coloured yellow. Being a lectin-like receptor, CD94–NKG2A is structurally more similar to mouse LY49 receptors than to human KIRs, but it binds to a different site on the MHC class I molecule from LY49 (REFS 101,102). The overlap in the binding sites for KIRs and CD94–NKG2A on MHC class I molecules does not result in competition between the two receptors, because CD94–NKG2A is restricted to interaction with HLA-E, whereas KIRs are restricted to interactions with HLA-A, HLA-B, HLA-C and HLA-G. Indeed, CD94–NKG2A and KIRs have complementary roles in natural killer (NK) cell biology, because the interaction of HLA-E with CD94–NKG2A is highly conserved, whereas the interactions between KIRs and HLA-A, HLA-B and HLA-C are highly diverse.

Co-evolution of MHC class I and KIRs

A comparison between different mammalian orders has revealed the rapid and convergent evolution of variable NK cell receptors[21]. A focus on simian primates shows the dynamic co-evolution between MHC class I molecules and KIRs. Because catarrhine primates (Old World monkeys, apes and humans) and platyrrhine primates (New World monkeys) have divergent sets of KIRs and MHC class I molecules[22], to gain perspective on the details of the human system of KIRs our focus can be further narrowed to the catarrhines, species that emerged only 20–38 million years ago[23].

In the human MHC locus on chromosome 6, the polymorphic genes *HLA-A*, *HLA-B* and *HLA-C* and the conserved gene *HLA-G* are the MHC class I genes that encode KIR ligands; we will call their counterparts in other catarrhine species *MHC-A*, *MHC-B*, *MHC-C* and *MHC-G*. The human KIR gene family is part of the leukocyte receptor complex (LRC) on chromosome 19 (REFS 24,25). Catarrhines have a common organization to the KIR locus[26] and share four phylogenetic lineages of KIRs (KIR lineages I, II, III and V) that are distinguished by their structure and their specificity for MHC class I molecules[27]. In humans, who have the most thoroughly studied system (FIG. 2), HLA-G is recognized by a lineage I KIR[28], whereas four mutually exclusive epitopes of the polymorphic HLA class I molecules are recognized by lineage II and III KIRs. Lineage II KIRs recognize the HLA-A epitope A3/11 and the Bw4 epitope of HLA-A and HLA-B. Lineage III KIRs recognize the C1 and C2 epitopes of HLA-C (HLA-C molecules containing these epitopes

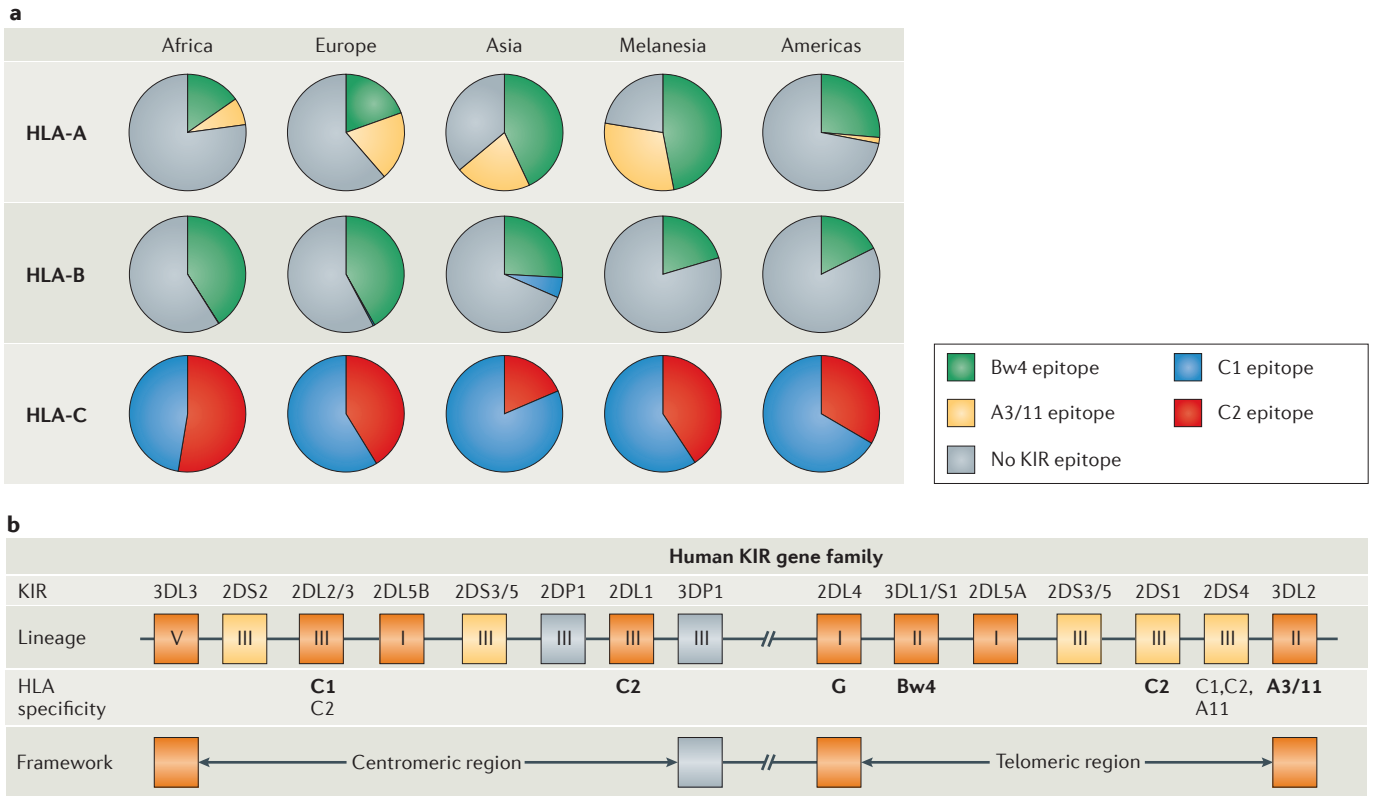


Figure 2 | **Humans KIRs recognize four epitopes of HLA-A, HLA-B and HLA-C.** **a** | The pie charts show the distribution of the four MHC class I epitopes that interact with killer cell immunoglobulin-like receptors (KIRs) in five human population groups. These four epitopes are mutually exclusive, so that each HLA-A, HLA-B or HLA-C allotype either has one of these epitopes or is not a ligand for KIRs (grey). The C1 epitope (blue) is carried by HLA-C allotypes with asparagine at position 80 and by certain HLA-B allotypes in Asian populations that have asparagine at position 80 and valine at position 76. The C2 epitope (red) is carried by HLA-C allotypes that have lysine at position 80. The Bw4 epitope (green) is carried by HLA-A and HLA-B allotypes that have arginine at position 83. The A3/11 epitope (yellow) is carried by two HLA-A allotypes, HLA-A*03 and HLA-A*11; recognition of this epitope by KIRs seems to be as peptide dependent as recognition by the αβ T cell receptor[103]. Data are pooled from a minimum of eight populations up to a maximum of fifty-five populations for each group shown. **b** | The upper linear diagram shows the order of the 15 human KIR genes in the KIR locus on human chromosome 19 and the phylogenetic lineages to which they belong (KIR lineage I, II, III or V). Beneath the gene boxes are shown the HLA class I epitope specificities of the encoded receptors. Non-bold type denotes a receptor that only recognizes some of the HLA allotypes carrying that epitope. The boxes for genes encoding inhibitory receptors are coloured orange, the boxes for genes encoding activating receptors are coloured yellow and boxes corresponding to pseudogenes are coloured grey. The lower linear diagram shows the framework genes and the centromeric and telomeric regions of gene-content variability that they flank and define.

are referred to here as HLA-C1 and HLA-C2, respectively) and two HLA-B allotypes that also carry the C1 epitope[29]. A ligand for lineage V KIRs has yet to be identified. Studies of the KIRs and MHC class I molecules of non-human catarrhines have provided insight into the order in which key components of the human system evolved and have shown how the KIR locus has co-evolved to keep up with changes in MHC class I genes.

Old World monkeys are phylogenetically the most divergent species from humans to have counterparts to human KIR ligands. In macaques, a multiplicity of MHC-A and MHC-B genes[30,31] and the presence of the Bw4 sequence motif[32] are associated with a corresponding range of lineage II KIRs[33–35]. Macaques lack MHC-C, and correspondingly have just one lineage III KIR, which might not recognize MHC class I molecules. Orangutans have many fewer MHC-A and MHC-B genes than macaques and only one lineage II KIR. This decrease in the number of lineage II KIRs and their ligands correlates with the emergence of *MHC-C* and the increased number of lineage III KIRs in orangutans[27]. The extent of the changes is impressive, because only ~50% of orangutan MHC haplotypes have the *MHC-C* gene, and all of their MHC-C allotypes carry only the C1 epitope. Because some orangutan, chimpanzee and human MHC-B allotypes carry the C1 epitope, and *MHC-C* evolved from an ancestral *MHC-B* gene, it is likely that the sequence encoding the C1 epitope arose in an *MHC-B* gene and was a feature of the gene that diverged to become *MHC-C*[36]. Thus, the C1 epitope functioned as a KIR ligand for several million years before the emergence of the C2 epitope and the fixation of *MHC-C* in a common ancestor of humans and chimpanzees[37]. Accompanying these events was a further increase in the number of lineage III KIRs: chimpanzees have nine lineage III KIRs and one lineage II KIR, and humans have seven lineage III KIRs and two lineage II KIRs[36].

The increasing complexity of the interactions between MHC-C molecules and lineage III KIRs reached its peak with chimpanzees, which have eight MHC-C-specific KIRs, including inhibitory and activating receptors for both the C1 and the C2 epitope[38] (FIG. 3a). By contrast, humans have only three KIRs specific for HLA-C: an inhibitory C1 receptor (either KIR2DL2 or KIR2DL3), an inhibitory C2 receptor (namely KIR2DL1)

and an activating C2 receptor (namely KIR2DS1). In addition, the activating receptor KIR2DS4, which is the only lineage III KIR common to humans and chimpanzees, recognizes some C1- or C2-bearing HLA-C allotypes, as well as the A3/11 epitope of HLA-A*11 (REF. 39). Three other activating lineage III KIRs that are expressed in humans (namely KIR2DS2, KIR2DS3 and KIR2DS5) once recognized HLA-C, but during the course of human evolution they have acquired mutations that block this function[40–42]. Finally, the human-specific gene *KIR2DP1* is a completely inactivated gene that once encoded an inhibitory C1 receptor. In contrast to the situation in humans, none of the chimpanzee lineage III KIRs has lost the capacity to recognize MHC class I molecules (FIG. 3a).

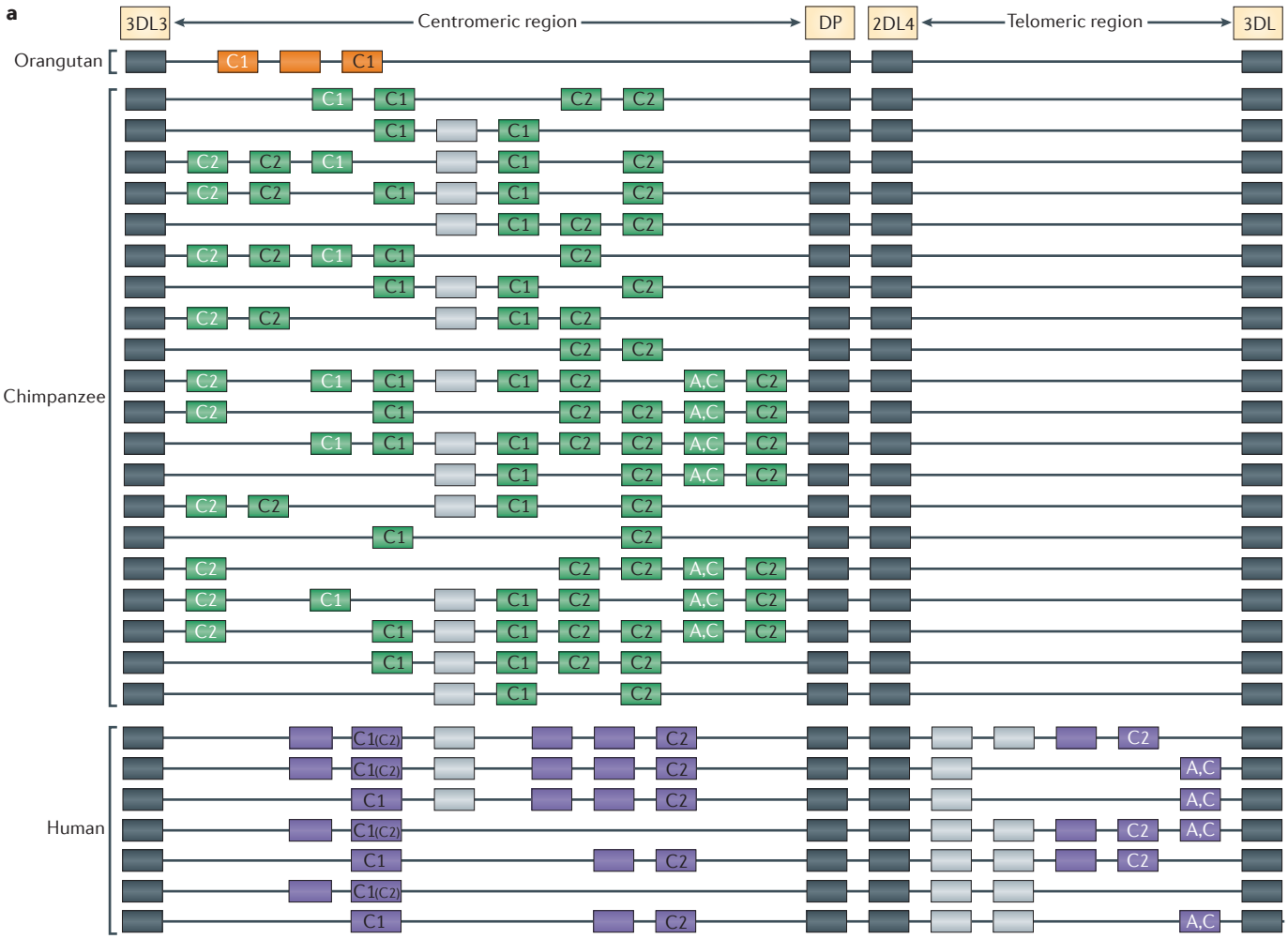


Figure 3 | **Co-evolution of HLA-C and KIR lineage III in hominids.** **a** | The organization and killer cell immunoglobulin-like receptor (KIR)-gene content of orangutan[27], chimpanzee[36] and human[46] KIR haplotypes are compared. Boxes representing the framework genes, which are common to all haplotypes, are shaded dark grey; boxes representing variable lineage I and II KIR genes are shaded light grey, and variable lineage III genes are shaded according to species: orange (orangutan), green (chimpanzee) and purple (human). For those lineage III KIRs that recognize MHC class I molecules, the epitope specificities are given in the gene box, using white script for activating KIRs and black script for inhibitory KIRs. With the exception of KIR2DS4 (the boxes labelled A,C), which is present in humans and chimpanzees, all of the variable lineage III KIR genes are species specific. **b** | The pie charts compare the distribution of the four MHC class I epitopes recognized by KIRs in chimpanzees and humans. The Bw4 epitope (green) originated in MHC-B. In chimpanzees, Bw4 is only carried by MHC-B allotypes, whereas in humans it was also transferred to HLA-A. The C1 epitope (blue) also originated in MHC-B and was directly inherited by MHC-C. Whereas chimpanzees retain C1 in both MHC-B and MHC-C molecules, in humans the C1 epitope has been largely eliminated from HLA-B. The C2 epitope (red) originated with MHC-C and remains exclusively an epitope of MHC-C in chimpanzees and humans. The A3/11 epitope (yellow) is specific to the human HLA-A*03 and HLA-A*11 allotypes, has not been correlated with polymorphisms in the HLA-A sequence, and seems to be highly peptide dependent[103].

Further distinguishing the human and chimpanzee systems is the distribution of the C1 epitope[36]. Approximately 25% of chimpanzee MHC-B variants retain the C1 epitope and function as ligands for C1-specific KIRs, whereas the human C1 epitope is almost exclusively associated with HLA-C (FIG. 3b). An obvious potential benefit to HLA-C becoming a specialized KIR ligand in humans is the relaxation of the pressure on KIRs to keep up with changes in HLA-A and HLA-B driven by $CD8^+$ T cells.

The KIR locus in gibbons (the lesser apes) does not conform with the progression observed in other catarrhines, in which a multiplicity of lineage II KIRs was replaced by a multiplicity of lineage III KIRs with the emergence and elaboration of *MHC-C*. In gibbons, the KIR locus has been subject to intensive deletion and mutation, causing a loss of structural integrity[43]. Targets for inactivation were lineage I and III KIRs, which in humans recognize HLA-G and HLA-C molecules, respectively. In accordance with the loss of these KIRs, the gibbon MHC locus lacks the genomic segments that carry *MHC-G* and *MHC-C* in hominids[31]. This decline of the KIR and MHC class I loci in gibbons is a clear demonstration of the transient nature and species specificity of variable NK cell receptors.

Evolution of two KIR haplotype groups

Crucial innovations in hominid evolution were the emergence of MHC-C molecules and the establishment of their C1 and C2 epitopes as dominant KIR ligands that are present in all human populations and maintained by balancing selection. Subsequently, and only during human evolution, the KIR haplotypes became divided into two groups, A and B, with qualitatively different KIR gene contents[26,44]. The A haplotypes, which encode mainly inhibitory KIRs that recognize HLA class I molecules, are more similar to the chimpanzee KIR haplotypes[36]. Uniquely human are the B haplotypes, which have accumulated genes encoding KIRs that have decreased or no binding to HLA class I molecules, such as KIR2DS2, KIR2DS3 and KIR2DS5 (REFS 45,46) (BOX 1). The differences between the KIR A and B haplotypes evolved in two stages. The first stage — involving the part of the haplotype closer to the chromosomal centromere (referred to here as the centromeric region of the haplotype) — occurred soon after the human and chimpanzee lines diverged ~5–7 million years ago. The part of the B haplotype closer to the telomere (referred to here as the telomeric region of the haplotype) evolved at a later time, ~1.7 million years ago[46], contemporaneously with the emergence of the genus *Homo* and of *Homo erectus*, the first ancestral human to achieve fully upright walking and to successfully migrate out of Africa to populate Eurasia[47,48].

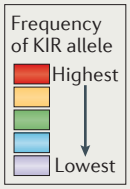
The KIR A and B haplotypes are present in all human populations[49] and are maintained by balancing selection[50]. This implies that the haplotype groups have to some extent become specialized for distinct and complementary functions. We believe that several lines of evidence point to these differences being associated with the involvement of NK cells in both immunity and reproduction.

KIRs, HLA-C and reproduction

Most cells of the body co-express HLA-A, HLA-B and HLA-C, but a crucial difference occurs in pregnancy, when extravillous trophoblast (EVT) cells express HLA-C but not HLA-A or HLA-B[51,52]. EVT cells are

Box 1 | KIR A and B haplotypes

Human killer cell immunoglobulin-like receptor (KIR) genes are evenly distributed between the centromeric and telomeric regions of the KIR locus. Both regions have alternative and distinctive gene-content motifs. This is exemplified in the figure by the range of motifs found in the Yucpa, a South Amerindian population that has been subjected to strong selection by infectious disease and population bottleneck[50]. Combination of the centromeric A1 and telomeric A1 motifs forms the KIR A haplotypes, which encode inhibitory receptors for HLA-C1 (KIR2DL3) and HLA-C2 (KIR2DL1) in the centromeric region and inhibitory receptors for HLA-Bw4 (KIR3DL1) and HLA-A3/11 (KIR3DL2) in the telomeric region. KIR2DS4, which recognizes HLA-A3/11 and some C1- and C2-containing HLA-C molecules, is the activating receptor of the A haplotypes. The different A haplotypes all have an identical KIR gene content, but they vary by allelic polymorphism. For each gene, the colours denote different alleles: the most frequent allele is shown in red, the next most frequent in yellow, and so on to green, blue and purple. The divergent allelic lineages for KIR2DL2 and KIR2DL3 (L2 and L3), KIR3DL1 and KIR3DS1 (L1 and S1) and KIR2DS4 (full-length (fl) and deletion (del) forms) are indicated: neither KIR3DS1 nor KIR2DS4del bind to HLA class I molecules. The Yucpa have five A haplotypes (A1–A5), constituting 45.9% of the total KIR haplotypes. Found at a similar frequency (47.5%), the KIR B1 haplotype (which comprises centromeric B2 and telomeric B1 motifs) has no allelic polymorphism. This haplotype lacks genes encoding inhibitory receptors for HLA-C2 and HLA-Bw4 and has a distinctive form of the inhibitory C1 receptor KIR2DL2 that cross-reacts with the C2 epitope. Further distinguishing the KIR B1 haplotype from KIR A haplotypes is the activating HLA-C2 receptor KIR2DS1 and five expressed KIRs that cannot recognize HLA class I molecules: the inhibitory receptor KIR2DL5 and the activating receptors KIR2DS2, KIR2DS5 and KIR3DS1. A repetitive sequence between KIR3DP1 and KIR2DL4 facilitates the recombination of centromeric and telomeric regions, yielding haplotypes that have centromeric A motifs with telomeric B motifs (haplotype B2) or centromeric B motifs with telomeric A motifs (haplotypes B3 and B4). Although they are at low frequency in the Yucpa, such recombinants are more frequent in some other populations. Because centromeric and telomeric B motifs dominate in studies of disease association, all haplotypes that have a centromeric or a telomeric B motif or both centromeric and telomeric B motifs are grouped together as KIR B haplotypes.



KIR haplotype	Motif: Centromeric	Motif: Telomeric	Centromeric region: 3DL3	2DS2	2DL2/3	2DP1	2DL1	3DP1	Telomeric region: 2DL4	3DL1/S1	2DL5A	2DS5	2DS1	2DS4	3DL2	Haplotype frequency (%)
A1	A1	A1			L3					L1				fl		22.1
A2	A1	A1			L3					L1				fl		9.0
A3	A1	A1			L3					L1				fl		7.4
A4	A1	A1			L3					L1				fl		4.1
A5	A1	A1			L3					L1				del		3.3
B1	B2	B1			L2					S1						47.5
B2	A1	B1			L3					S1						4.1
B3	B2	A1			L2					L1				del		1.6
B4	B2	A1			L2					L1				fl		0.8

cells of fetal origin that invade the mother's uterus, where they transform the spiral arteries into large vessels capable of conducting sufficient blood to the placenta until the end of pregnancy[53] (FIG. 4). The extent of arterial transformation by trophoblast cells affects the success of reproduction. Defective transformation by EVT cells, resulting in insufficient blood supply to the placenta, can lead to pre-eclampsia, stillbirth or low birth weight. However, it is also important that babies do not become too big, because this can lead to damaging and even fatal complications during childbirth. Trophoblast invasion must therefore be controlled. This is the probable function of uterine NK cells, which dominate the uterine leukocyte population[54–58] and preferentially express HLA-C-specific KIRs[59].

Contact, communication and cooperation between EVT cells and uterine NK cells could involve the recognition of HLA-C, HLA-E and HLA-G molecules on EVT cells by their cognate receptors on uterine NK cells. Of these interactions, which involve both activating and inhibitory receptors, only those between HLA-C molecules and KIRs are polymorphic and influence the course of pregnancy in a genetically determined manner[60]. At highest risk for miscarriage, pre-eclampsia and fetal growth restriction — syndromes that are associated with an insufficiently invasive placenta — are mothers homozygous for KIR A haplotypes and HLA-C1, carrying a fetus that has inherited HLA-C2 from the father[61–63]. In this combination, the mother has the inhibitory C2 receptor (KIR2DL1) but not its activating counterpart (KIR2DS1). Thus, the inhibition of uterine NK cells (mediated by the recognition of fetal HLA-C2 by KIR2DL1) is implied as a mechanism causing insufficient uterine invasion by EVT cells. In this model, we postulate that the inhibited NK cells would provide insufficient help, by way of cytokines and cell–cell contacts, to the EVT cells.

Women can be protected against these pregnancy disorders by KIR B haplotypes, particularly their telomeric region[61]. Among the KIRs encoded by the telomeric region of the B haplotypes is KIR2DS1, the activating C2 receptor, which can counter the inhibitory effects of KIR2DL1 (BOX 1). The centromeric region of the B haplotypes

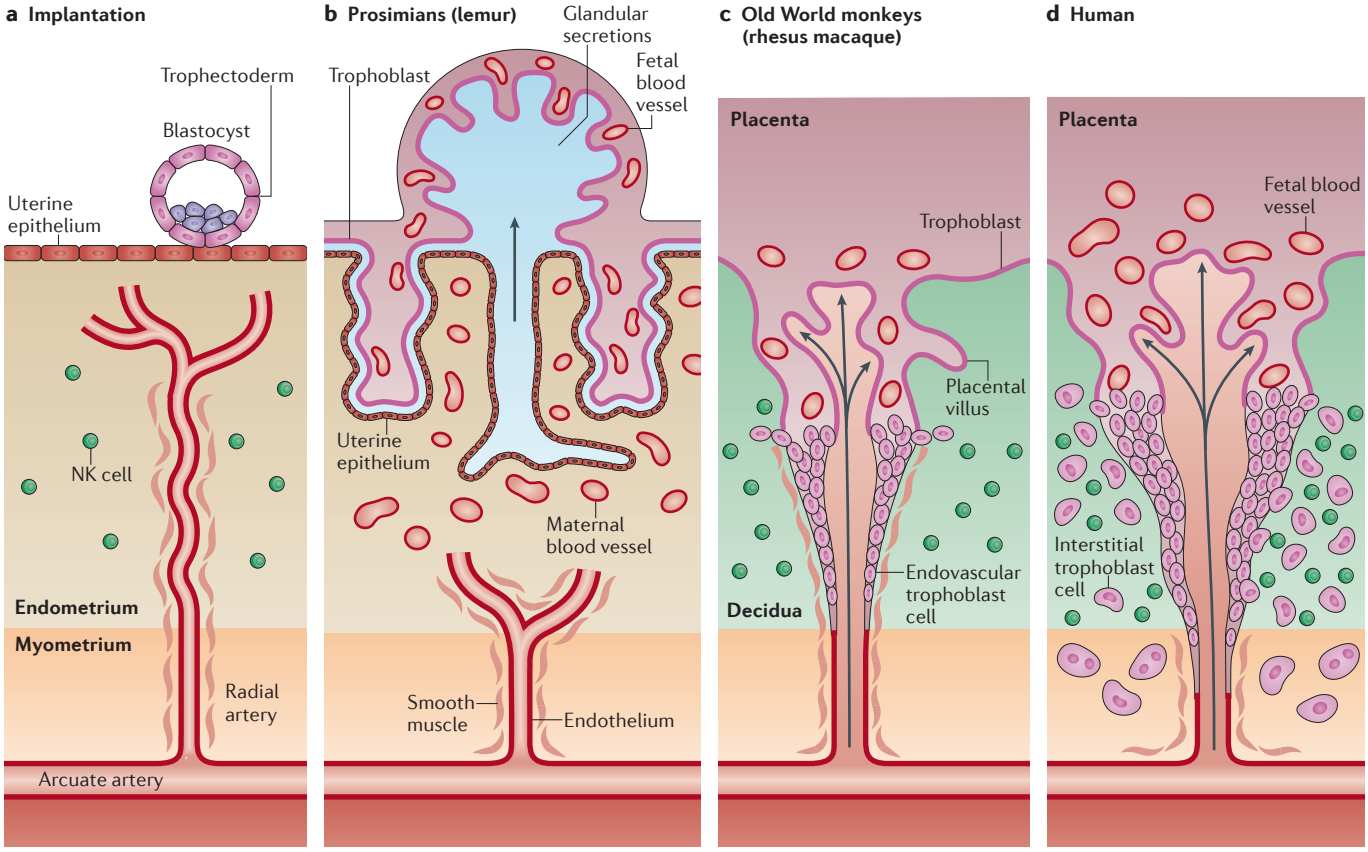


Figure 4 | **Increased placental invasion of the uterus in primates is associated with the presence of NK cells.** **a** | This panel shows the implantation of the blastocyst, an early stage in embryo development, into the uterine epithelium. Cooperative interactions between trophoblast cells and maternal cells then form the placenta. **b** | In prosimians, such as the lemur, the trophoblast cells lie adjacent to the surface epithelium of the uterus but they do not invade it. Neither are natural killer (NK) cells present. Nutrients are transferred to the fetus from maternal blood vessels close to the uterine epithelium and in glandular secretions. This arrangement is known as an epitheliochorial placenta. The endometrium does not transform into the decidua, which is the name given to endometrium that has differentiated under the influence of progesterone. **c** | In Old World monkeys, such as the rhesus macaque, trophoblast cells penetrate through the epithelium and invade maternal arteries, where the trophoblast cells replace the vascular endothelial cells. This transformation increases the blood supply to the placenta, where nutrients are transferred directly across the placenta from maternal blood to the fetal capillaries. Accompanying these changes is the presence of NK cells in the decidua. This type of placenta, which is also seen in human pregnancy, is called a haemochorial placenta. **d** | In human placentation, trophoblast cells invade the blood vessels as in rhesus macaques, but they replace the vascular endothelium in the myometrium to a greater degree. The invasion extends beyond the endometrium into the myometrium, whereas it is restricted to the endometrium in rhesus macaques. In addition, trophoblast cells invade the decidua, replacing the medial smooth muscle with fibrinoid material. Accompanying these changes is the presence of numerous NK cells.

can also contribute to protection, as some B haplotypes lack *KIR2DL1* (BOX 1) and the others have alleles encoding 'weak' forms of KIR2DL1. For example, KIR2DL1*003, the most common KIR2DL1 allele in A haplotypes, has stronger signalling function[45] and higher avidity for HLA-C2 (H. Hilton and P.P., unpublished observations) than does KIR2DL1*004, the common B haplotype allele[46]. In addition, KIR2DL3, the inhibitory C1 receptor of A haplotypes, is replaced in B haplotypes by a combination of the inhibitory receptor KIR2DL2, a stronger receptor for C1 that cross-reacts with C2[29,42], and the activating receptor KIR2DS2, which does not recognize HLA class I molecules. Together, KIR2DL2 and KIR2DS2 function to decrease the frequency of NK cells expressing the inhibitory receptor KIR2DL1, a competitive effect that could arise because both KIR2DL2 and KIR2DL1 recognize HLA-C2 but KIR2DL2 is expressed before KIR2DL1 during the differentiation and education of NK cells[64]. Thus, by a variety of mechanisms, the KIRs of B haplotypes decrease the influence of the 'strong' inhibitory forms of KIR2DL1 that are carried by A haplotypes and are associated with pregnancy syndromes such as pre-eclampsia.

Obstructed labour, caused by babies too big to pass through the birth canal, is another potentially fatal complication of pregnancy. Having very large babies (>95th percentile) correlates with the presence of telomeric region genes of B haplotypes (and thus the activating receptor KIR2DS1) in the mother and of paternally derived HLA-C2 in the fetus[65] (S. Hiby and A.M., unpublished observations). The implication is that, in these pregnancies, KIR2DS1-mediated NK cell activation might give too much help to EVT cells and promote overly deep placental invasion. Thus, KIR B haplotypes can confer both advantage and disadvantage in pregnancy; this is also the case for the A haplotypes, because of the allelic relationship between the two haplotype groups. We believe that such correlations are consistent with the human KIR A and B haplotype dichotomy having evolved under selective pressure from reproduction. Evidence for this type of selection is provided by the worldwide inverse correlations between HLA-C2 and KIR A haplotype frequencies[63] and between HLA-C1 and KIR B haplotype frequencies[66]. This situation reduces the frequency of pregnancies at risk for pre-eclampsia, which is highest when mothers homozygous for KIR A haplotypes bear HLA-C2$^+$ babies.

Striking the KIR haplotype balance

Human KIR A haplotypes combine a fixed gene content with receptors that have a high degree of polymorphism, which modulates the functional recognition of HLA-A, HLA-B and HLA-C epitopes and distinguishes human populations. These are characteristics of immune-system molecules that detect pathogens and become subject to the strong selection pressures that the pathogens exert. Consistent with this thesis, resistance to acute hepatitis C virus (HCV) infection correlates with genotypes that are homozygous for a KIR A haplotype and HLA-C1 (REFS 67,68). This is a stringent test, because HCV is a virus against which most human immune systems are ineffective. A minority (20–30%) of individuals terminate acute HCV infection, whereas the majority develop a debilitating chronic infection, which is associated with an increased risk of liver cancer[69]. KIR A haplotype homozygosity is also associated with resistance to acute Ebola virus infection[70] and, in combination with HLA-C1 homozygosity, a favourable response to treatment for chronic HCV infection. Although few acute infections have been studied for KIR association, the results suggest that KIR A haplotypes can provide more effective immunity against acute viral infections than KIR B haplotypes, which have an accumulation of attenuated and less polymorphic KIRs.

In our opinion, that homozygosity for HLA-C1 and KIR A haplotypes is associated with both resistance to HCV infection and susceptibility to pre-eclampsia can be seen as evidence for the compromise made, during the evolution of the KIR A and B haplotypes, between the functions that NK cells exert in immunity and reproduction. Illustrating how this might have worked is the cyclical model shown in FIG. 5a. When an epidemic infection passed through a population, causing disease, death (particularly of the young) and social disruption, selection favoured KIR A haplotypes over KIR B haplotypes and HLA-C1 over HLA-C2. When the epidemic subsided, the surviving and now smaller population was immune to further infection and enriched for KIR A haplotypes and HLA-C1, with a corresponding reduction in KIR B haplotypes and HLA-C2 epitopes. At this juncture, survival of the current generation was no longer the issue, and the priority became production of the next generation. In this second phase of the cycle, selection favoured KIR B haplotypes and HLA-C2, factors that enhance the generation of larger and more robust progeny. Because human history has always involved successive cycles of the type shown in FIG. 5a, this alternating pattern of selection pressures has been persistent. That all extant human populations maintain significant frequencies of both KIR A and KIR B haplotypes (FIG. 5b) as well as of HLA-C1 and HLA-C2 shows that all have been necessary for the survival of human populations, although none of them is essential for the health and survival of individuals.

Glossary

Adaptive introgression
The process by which a mating between two species, or two geographically or culturally separated populations, leads to the acquisition of functionally advantageous gene variants. Under natural selection these new variants rise to much higher frequency in their new 'home' species than genes that provide little or no advantage.

Balancing selection
For certain genetic traits there are two or more alternative forms that provide complementary functions that are sufficiently valuable that they are maintained as a balanced polymorphism in the population. The most obvious example of a balanced polymorphism is that between X and Y chromosomes. Without both women (XX) and men (XY) a population cannot survive to the next generation. HLA class I, KIR and numerous other immune-system genes are maintained as balanced polymorphisms.

Genetic drift
A process associated with small populations in which random events, as opposed to natural selection, lead to a polymorphic variant either rising to high frequency and being fixed or being driven to low frequency and eliminated from the population.

KIR lineages I, II, III and V
The evolution of gene families of the immune system is always associated with the individual members acquiring functional and structural differences that define different phylogenetic lineages. In the KIR gene family the different lineages are associated with recognition of different MHC class I ligands.

Population bottlenecks
Periods during which a population suffers a substantial reduction in size, and as a consequence loses potentially valuable genetic diversity. Epidemics of infectious disease and conflicts between warring populations can create population bottlenecks.

Prosimian primates
Modern primate species, such as lemurs and lorises, that more closely resemble ancestral primates than do the simian primates. With the exception of the Madagascar lemurs, they have largely been replaced by the simian primates and the extant species are nocturnal.

Simian primates
Simian primates comprise monkeys, apes and humans. They are characterized by good eyesight and flexible hands and feet. The only nocturnal species of simian primate are the owl monkeys (*Aotus* spp.) of South and Central America.

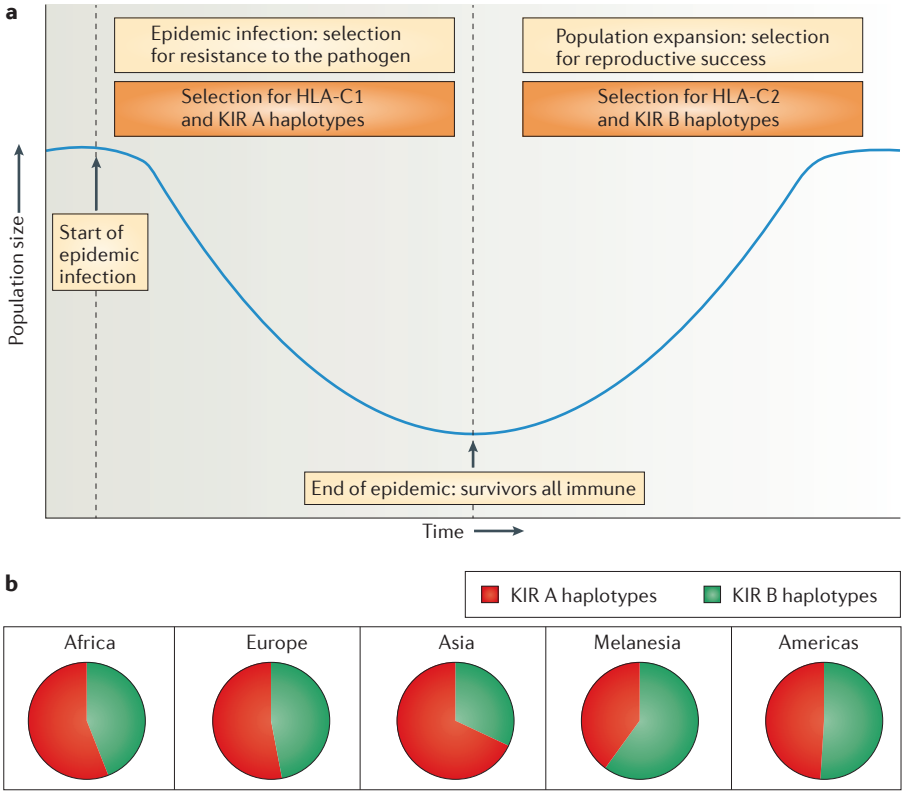


Figure 5 | **Model for the maintenance of KIR A and B haplotypes and HLA C1 and C2 epitopes in human populations.** **a** | This panel shows a hypothetical cycle in which the size of a population changes over time and circumstance. With the onset of an epidemic of an acute and lethal viral infection, the population size will progressively decrease, disproportionately so for infants and the younger generation. If the combination of killer cell immunoglobulin-like receptor (KIR) A haplotypes and HLA-C1 molecules provides resistance to infection, then the surviving population (which will be largely immune to further infection) will have increased frequencies of KIR A haplotypes and HLA-C1 and decreased frequencies of KIR B haplotypes and HLA-C2 compared with the starting population. With the end of the infectious cycle, the challenge becomes one of reproduction, as the population can survive only if the next generation is sufficiently viable and numerous. In this situation, when there is a strong element of competition between the survivors for limited resources, there will be selection for the combination of KIR B haplotypes and HLA-C2 molecules, which are the most recently evolved elements of the system of interactions between KIRs and HLA class I molecules. Pregnancies in which the mother has a KIR B haplotype and the fetus has HLA-C2 are predicted to favour larger and more robust progeny. Thus, in this part of the cycle, the frequencies of KIR B haplotypes and HLA-C2 will increase, whereas those of KIR A haplotypes and HLA-C1 will decrease. **b** | All human populations retain KIR A haplotypes (red) and KIR B haplotypes (green), but their relative frequencies vary.

Bigger brains and KIR B haplotypes

Since the ancestors of humans and chimpanzees separated 5–7 million years ago, chimpanzees have diverged less from the common ancestor, while remaining in equatorial Africa[48,71,72], whereas humans have diverged further, while expanding their range throughout the world's landmass[73]. The emergence of KIR B haplotypes was a part of this human-specific evolution and possibly reflects changes in locomotion, anatomy and reproduction. That chimpanzees did not undergo such changes could explain why their KIR locus was not selected to form two haplotype groups as a means of improving reproductive success.

A key human innovation was bipedalism. Whereas chimpanzees mainly use all four limbs to knuckle walk, adult humans walk fully upright on two legs. This development (which was largely achieved by 3.66 million years ago[74]) required considerable anatomical changes that altered the size and shape of the human female pelvis and the dimensions of the birth canal. When they first evolved, these pelvic changes would not have affected obstetric mechanics, but with the evolution of increasingly bigger brains problems began to arise. The size of the human baby's head increased until it reached the limit defined by the birth canal. Thus, at full term, a modern human baby's head just fits into the birth canal, whereas chimpanzee babies have the luxury of more headroom. In the course of human evolution, birthing became a difficult, dangerous and frequently fatal process, requiring rotation of the baby to pass through the pelvis and obligatory assistance from a midwife[75–77].

The development of bigger brains required more nourishment *in utero*, putting greater demands on the blood supply to the placenta[78,79]. This was achieved by increasing the extent to which the placenta invades the uterine arteries, a process that is mediated by EVT cells and thought to be regulated by uterine NK cells. Prosimians have a non-invasive placenta, whereas in gibbons and Old World monkeys the uterine arteries are modified by trophoblast cells, which migrate down the inside of the arterial walls from the placenta (FIG. 4). This also occurs in hominids, but in addition trophoblast cells invade through the stroma to penetrate deep into the myometrium, where they surround and destroy the medial smooth muscle, reconstructing the arteries with fetal cells[80]. The evolution of this deep placental invasion correlates with the emergence of MHC-C and cognate KIRs, in line with the potential role of these molecules in the regulation of EVT cells by uterine NK cells. That MHC-C1 and activating and inhibitory C1-specific KIRs evolved first (before MHC-C2 and C2-specific KIRs) suggests that their interactions contributed to deeper placental invasion in ancestral hominids. Subsequently, in a common ancestor of humans and African apes, we suggest that increasing brain size and the associated risk of death during childbirth favoured the evolution of MHC-C2 and both activating and inhibitory C2-specific KIRs. The resulting bipartite system strikes a balance that reduces the likelihood of too little or too much placental invasion.

At full term, the human brain is about twice the size of the chimpanzee brain[81]. Most of this increase in human brain size occurred gradually over the past 2 million years, a progression seen in specimens of *Homo erectus*[47,48] that correlates with the emergence of the telomeric region of the KIR B haplotypes ~1.7 million years ago[46]. A key component of this telomeric region — the activating C2-specific receptor KIR2DS1 — is seen today to protect against recurrent miscarriage, pre-eclampsia and low birth weight. However, at earlier times in human evolution, when the heads of human babies were smaller than the birth canal, it could have helped to increase human brain size by enhancing NK cell-mediated help to trophoblast cells and thereby increasing placental invasion. Consistent with this mechanism, KIR2DS1 is over-represented among

mothers who have large babies that cause obstructed labour (S. Hiby and A.M., unpublished observations). The centromeric region of the KIR B haplotypes emerged before the telomeric region, shortly after the human and chimpanzee lines diverged 5–7 million years ago[46]. The lower level of protection against recurrent miscarriage, pre-eclampsia and low birth weight provided by the centromeric region of the KIR B haplotypes compared with the telomeric region correlates with the smaller increase in brain size that occurred in the human line of australopithecines before the emergence of the genus *Homo*[48].

Maintaining diversity during migrations

Upright walking and an increasingly bigger brain contributed to the success of *Homo erectus* in extending its range out of Africa and populating Eurasia between ~1.8 and ~0.3 million years ago. Similar migration and colonization events have occurred on at least two other occasions since. The first, ~600,000 years ago, was by ancestors of the Neanderthals (*Homo neanderthalensis*). The Neanderthals emerged in Europe ~300,000 years ago and survived in Eurasia until ~30,000 years ago[82]. The second occurred ~67,000 years ago and was by anatomically modern humans (*Homo sapiens*), who emerged in Africa ~200,000 years ago[83]. After reaching Eurasia they outlived the archaic human populations and went on to colonize much of the Earth's landmass[84].

In present-day human populations, genetic diversity decreases with the distance of migration from Africa[85]. This steady loss of diversity is the consequence of passage through a succession of population bottlenecks as migrant groups settled into new territories and expanded their populations. With population growth came competition for resources and resulting conflict that could split the population: one part staying put; the other forced out to continue migration[73,86]. Both factions emerging from such episodes could have less genetic diversity than the original combined population. Other genetic bottlenecks would have accompanied periods of hardship, when the population size decreased owing to factors such as infection, famine, drought and warfare (either individually or in combination, as has often occurred).

HLA class I molecules and KIRs are encoded by polymorphic gene families that, by diversifying the immune systems of individuals within a population, increase the probability that the population will survive the successive epidemics of infectious disease caused by diverse and rapidly evolving pathogens. For such genes, which have no 'wild-type' alleles, the effects of population bottlenecks are potentially catastrophic, because variants not under immediate selection can be irretrievably lost. This has raised an important question: how much diversity in HLA class I molecules and KIRs has been necessary for human populations to survive? Possible answers to this question can be obtained by studying present-day indigenous populations.

The Americas were the last continents to be populated by modern humans. Asian migrants from Siberia arrived in Alaska ~17,000 years ago and then extended their range by southward migration throughout North and South America[87]. South Amerindian populations have the least genetic diversity of all modern human populations on a genome-wide level, as exemplified by their loss of polymorphism in the ABO system of blood group antigens[88]. Although HLA class I diversity also decreases to some extent with distance from Africa, substantial diversity is retained by South Amerindian populations[89,90], which have 4–6 allotypes of HLA-A, HLA-B and HLA-C, including ones that carry the C1, C2 and Bw4 epitopes recognized by KIRs. Replenishing lost diversity are new variant alleles (particularly *HLA-B* alleles) that were derived by recombination between the alleles that were present in the Asian migrants from Siberia[91–94] (FIG. 6a). The KIR genes of South Amerindians present a similar picture. With the exception of *KIR2DS3* in some tribes, such as the Yucpa (BOX 1), South Amerindians retain all of the major KIR genes found worldwide, as well as a balance between KIR A and B haplotypes, and have several alleles of the polymorphic KIR genes, including some new variant alleles. That such sets of KIRs and HLA class I molecules were maintained despite numerous population bottlenecks suggests they represent the minimal diversity necessary for human populations to survive over periods of more than 10,000 years. The corollary being that any population lacking such diversity either died out or was assimilated into another population. Notably, the HLA-A epitope A3/11, which is recognized by KIRs, was not necessary for the survival of Amerindians (FIG. 2).

Modern migrants acquired archaic HLA

When modern humans first populated the Americas, their only source of additional HLA class I and KIR diversity was new variant alleles formed by point mutation or recombination. For the modern humans who migrated out of Africa ~67,000 years ago, another potential source of genetic diversity was the existing Eurasian populations of archaic humans, notably the Neanderthals, with whom they overlapped for ~30,000 years[95,96]. Whole-genome comparisons show that modern humans did indeed meet and mate with archaic humans, giving rise to viable offspring who passed their Neanderthal genes on to their modern human descendants in Eurasia, a process known as introgression. The overall Neanderthal contribution to present-day Eurasian genomes is thus estimated to be 1–4%[97]. The Neanderthal woman whose genome has been sequenced was heterozygous for *HLA-A*, *HLA-B* and *HLA-C* and carried alleles that are identical to common alleles in the present-day Eurasian population[98]. Her HLA type included the C1, C2 and Bw4 epitopes, but not the A3/11 epitope. Within the present-day human population, the two HLA haplotypes and some of the alleles found in the Neanderthal woman are present in Eurasia but absent from Africa. Genetic elements with this geographical distribution — for example HLA-C*07:02 (which has the C1 epitope) and HLA-C*16:01 (which has the C2 epitope) — are unlikely to have come out of Africa with migrating modern humans and are more likely to have been acquired from Neanderthals in Eurasia through introgression[98]. Importantly, the frequencies of introgressed HLA class I alleles in present-day Eurasian populations are much greater than the 1–4% genome average for introgressed Neanderthal genes[97], which indicates that they were functionally beneficial and were driven to higher frequencies by natural selection, a process known as adaptive introgression. This process would have been a much more efficient way for migrant modern humans to replenish lost HLA class I diversity (including lost ligands for KIRs) than selecting for new recombinants and point mutants, because one mating could introduce a full set of new and distinctive HLA-A, HLA-B and HLA-C allotypes that had already stood the test of time in a human population in the Eurasian environment. For example, HLA-B*73 is an unusually divergent *HLA-B* allele of archaic origin that entered the modern human population in western Asia[98] (FIG. 6b). Whereas the new variants that evolved in South America differed from the original genes by 1–3 amino acid substitutions, the hypothetical acquisition of HLA-B*73 by these populations would have given them a new variant with 41 amino acid substitutions, 16 of which were at positions of functional importance (FIG. 6c).

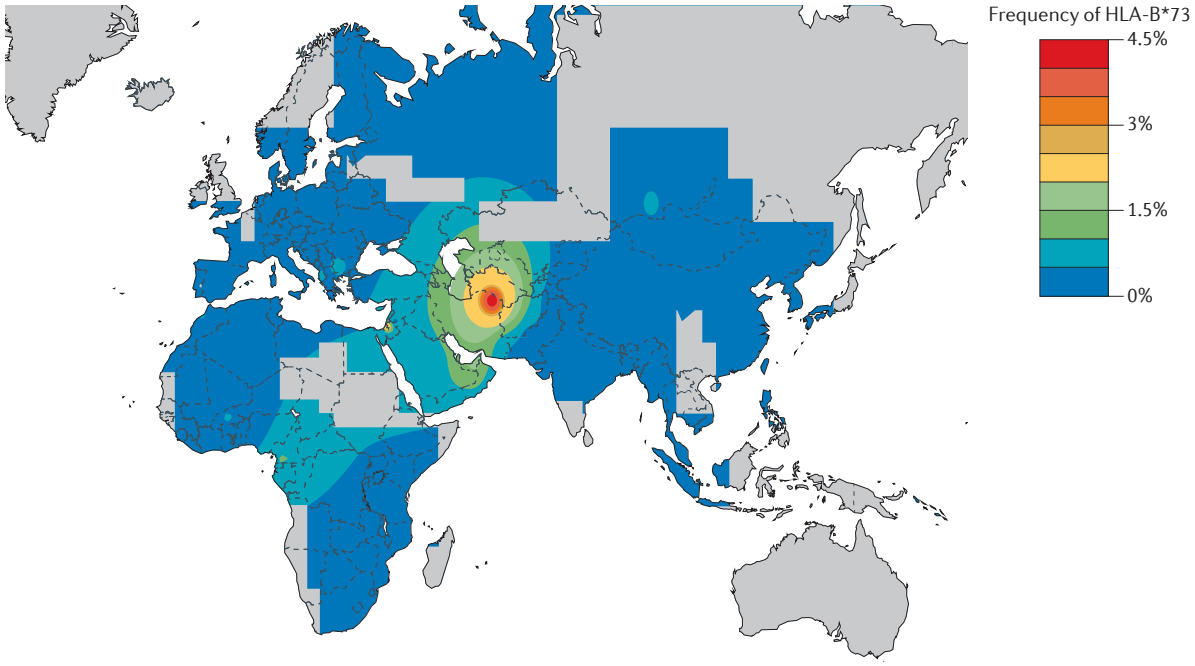
The genome sequence of a Denisova hominin suggests that this recently discovered type of archaic human also overlapped with modern humans, over a broad geographical

a

HLA-B*35:01

Domain	α_1			α_2										Potential donor HLA-B alleles				
Function	*p*	*t*	*p*		*p*	*p*		*p*	*p*	*pt*	*p*	*pt*	*p*					
Position	45	63	67	94	95	97	103	114	116	152	156	163	171	B*15:01	B*39:01	B*40:02	B*48:01	B*51:01
B*35:01	T	N	F	I	I	R	L	D	S	V	L	L	Y					
B*35:04								N	Y									
B*35:05				T	L	S												
B*35:06								N	F									
B*35:10		E																
B*35:11										E								
B*35:12							V	N	Y									
B*35:14										E	W							
B*35:15												E						
B*35:16		E				S	V											
B*35:17						S	V											
B*35:19	K																	
B*35:20			S															
B*35:21										E			H					

b



c

Domain	Signal sequence					α_1														α_2																α_3						Stem, transmembrane and cytoplasmic regions							
Function									*p*	*p*	*p*	*tk*	*pt*		*pt*	*tk*	*p*				*p*	*p*		*p*	*p*	*p*		*pt*	*p*							*l*															
Position	-23	-21	-11	-10	-8	9	11	12	24	45	67	69	70	71	74	76	77	90	94	95	97	103	113	114	116	131	163	171	194	239	253	267	268	270	275	295	297	299	ins	301	306
HLA-B*35:01	R	T	W	G	V	Y	A	M	A	T	F	T	N	T	Y	E	S	A	I	I	R	L	H	D	S	S	L	Y	V	R	E	P	K	L	E	A	V	I		G	T
HLA-B*73:01	L	M	S	A	L	H	S	V	T	E	C	A	K	A	D	V	G	D	T	W	T	M	Y	N	F	R	E	H	I	G	Q	Q	E	C	K	V	T	A	V	V	A

Figure 6 | **Maintaining HLA diversity during migrations that increased the geographical range of human species. a** | Humans first entered the Americas at Alaska after migration from Asia ~17,000 years ago. North, Central and South America were then colonized by southward migration. The *HLA-B* alleles of present-day Native American populations of North America largely remain identical to those that came with the migrants from Asia. However, in the southwestern part of the United States and increasing with distance southwards, the Amerindian populations have 'new' recombinant *HLA-B* alleles in which a short sequence segment in one Asian founder allele is replaced by the homologous segment from another founder allele. This phenomenon is illustrated for the HLA-B*35:01 Asian allele. Shown are 13 Amerindian recombinants of HLA-B*35:01, the amino-acid positions that were affected by the recombinations, and the various founder alleles that could have been the donors for the recombinations. All of these recombinations result in one or more amino-acid substitutions in the α_1 and α_2 domains that alter the interactions of HLA-B with antigenic peptides (*p*) and/or T cell receptors (*t*). For each recombination the potential donor alleles are indicated by the coloured boxes on the right and the donated sequences by the coloured residue boxes on the left. For the six recombinations with more than one possible donor, the residues are only shaded with the colour of one of them (the one furthest to the left). **b** | The 'heat map' shows the geographical distribution of the archaic allele HLA-B*73 (REF. 98). The colour spectrum denotes increasing frequency from 0% (dark blue) to 4.5% (bright red). Grey shading indicates regions for which high-resolution HLA typing data from ethnically well-defined indigenous populations are not available. **c** | The table shows the 41 amino-acid differences that distinguish HLA-B*35:01 and HLA-B*73:01. Of these, 16 are at functionally important positions that make contact with the peptide (*p*), T cell receptor (*t*), killer cell immunoglobulin-like receptor (*k*) or leukocyte immunoglobulin-like receptor (*l*).

range from Siberia to Southeast Asia[99]. In present-day genomes, the Denisovan contribution is highest in Melanesia, where it reaches 4–6%[99]. The Denisovan woman whose genome has been sequenced was heterozygous for *HLA-A*, *HLA-B* and *HLA-C*, and carried *HLA-A* and *HLA-C* alleles that are common in present-day Southeast Asian and Melanesian populations. By contrast, her *HLA-B* alleles are rare or absent in present-day populations, but appear as recombinants of common present-day *HLA-B* alleles[98]. Included in the Denisovan HLA type are all four epitopes recognized by KIRs: C1, C2, Bw4 and A3/11. Within the present-day population, the two HLA haplotypes and some of the alleles of the Denisovan woman are present in Southeast Asia and Melanesia, but absent from Africa. Moreover, their frequencies are indicative of adaptive introgression. Notably, HLA-A*11 reaches frequencies of 64% in Melanesia. At the *HLA-A* locus, for which the data are the most comprehensive, analyses of the distribution and linkage disequilibrium in present-day populations estimate the contribution of archaic *HLA-A* alleles to non-African populations to be 50–95%[98]. The unexpected extent of this adaptive introgression raises the fascinating possibility that the acquisition of polymorphic immune-system and reproductive-system genes from archaic humans was necessary for the survival and success of some modern human populations outside of Africa.

Concluding remarks

In this article, we have drawn on observations from the fields of immunology, genetics, reproduction, anthropology and comparative anatomy to give a speculative working model that describes the contribution of variable NK cell receptors and their MHC class I ligands to human evolution. The model can also explain why these molecules have evolved to be different from their counterparts in other hominid species. Functional interactions between polymorphic MHC class I molecules and variable αβ T cell receptors have been maintained for more than 500 million years. By contrast, systems of variable NK cell receptors that recognize polymorphic MHC class I molecules are inherently unstable, are shorter lived and have evolved by convergence in placental mammals on several occasions. Underlying this instability are the competing demands of the functions that NK cells carry out in innate immunity, adaptive immunity and placental reproduction. The human KIR system of variable NK cell receptors has counterparts only in the simian primates, and exhibits extraordinary interspecies and intraspecies variation. KIRs co-evolved with MHC-A, MHC-B, MHC-C and MHC-G molecules in the catarrhine primates, and the emergence in hominids of MHC-C molecules provided a major source of polymorphic KIR ligands and the only ones expressed by EVT cells. During the formation of the placenta, these cells invade the uterus to remodel the maternal blood vessels that will supply the placenta with blood and nourish the fetus throughout the pregnancy. This process seems to be controlled by cooperative interactions between trophoblast cells and maternal NK cells in the uterus, and it is diversified within hominid populations by polymorphic interactions between MHC-C molecules on trophoblast cells and KIRs on uterine NK cells. The increase in brain size during hominid evolution necessitated deeper placental invasion of the uterus in pregnancy and selected for increased variation in MHC-C molecules and cognate KIRs. Unique to human evolution was the acquisition of upright walking, which facilitated migration out of Africa and further increases in brain size. Also associated with these developments, and unique to human species, was the formation of two groups of KIR haplotypes. These complementary KIR A and B haplotypes are maintained in all human populations and seem to represent a historical compromise between the immunological and reproductive functions of NK cells that was driven by selective pressure on the nervous system for bigger and better brains. The migration of modern human populations out of Africa to populate other continents was associated with the maintenance of a minimal, essential set of KIR and HLA class I variants. One way that modern humans replenished the genetic diversity lost in population bottlenecks was through the selection of new variants arising *de novo*; another, and possibly more effective, mechanism was to acquire old variants by mating with archaic humans.

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