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Missing or altered self: human NK cell receptors that recognize HLA-C

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Abstract

Natural killer (NK) cells are fast-acting and versatile lymphocytes that are critical for innate immunity, adaptive immunity and placental development. Controlling NK cell function are interactions between killer-cell immunoglobulin-like receptors (KIRs) and their HLA-A, -B and -C ligands. Due to the extensive polymorphism of both *KIR* and *HLA class I*, these interactions are highly diversified and specific combinations correlate with protection or susceptibility to a range of infectious, autoimmune and reproductive disorders. Evolutionary, genetic and functional studies are consistent with the interactions between KIR and HLA-C being the dominant control mechanism of human NK cells. In addition to their recognition of the C1 and C2 epitopes, increasing evidence points to KIR having a previously unrecognized selectivity for the peptide presented by HLA-C. This selectivity appears to be a conserved feature of activating KIR and may partly explain the slow progress made in identifying their HLA class I ligands. The peptide selectivity of KIR allows NK cells to respond, not only to changes in the surface expression of HLA-C, but also to the more subtle changes in the HLA-C peptidome, such as occur during viral infection and malignant transformation. Here we review recent advances in understanding of human-specific KIR evolution and how the inhibitory and activating HLA-C receptors allow NK cells to respond to healthy cells, diseased cells and the semi-allogeneic cells of the fetus.

Keywords

HLA class I; KIR; antigen presentation; genetic polymorphism; host-pathogen interactions; modern human migration; natural killer cells

Introduction

Natural killer (NK) cells are lymphocytes that are critical to the early phase of an immune response, for antibody-dependent cytotoxicity (ADCC) and development of the placenta in early pregnancy (Parham and Moffett 2013). The response of NK cells to infected, cancerous or semi-allogeneic tissue is guided by interactions between activating or

inhibitory NK cell receptors and major histocompatibility complex (MHC) class I ligands (known as HLA class I in humans). These direct interactions enable NK cells to distinguish healthy cells from diseased cells, which commonly have altered expression or abnormal forms of MHC class I.

In mammalian species, NK cell receptors typically comprise a bipartite system. This combines conserved receptors that recognize non-polymorphic MHC class I with diverse receptors that recognize polymorphic MHC class I (Guethlein et al. 2015). In humans, HLA-E binds a restricted set of peptides, which are largely derived from the leader sequences of the polymorphic HLA class I molecules, and thus forms the ligand for CD94:NKG2 lectin-like receptors (Braud et al. 1998; Horowitz et al. 2016). Because both receptor and ligand are genetically conserved, these interactions are a constant feature of human immune responses. In contrast, polymorphic HLA-A, B and C bind a diverse repertoire of peptides and are recognized by the killer-cell immunoglobulin-like receptors (KIR). Because both HLA-A, B and C and KIR are highly polymorphic, their interactions diversify and individualize NK cell responses (Valiante et al. 1997). The functional importance of these diverse interactions is illustrated by the association of various combinations of *KIR* and *HLA class I* with the outcome of infection (Alter et al. 2011; Holzemer et al. 2015; Khakoo et al. 2004; Wauquier et al. 2010), susceptibility to autoimmune disease (Luszczek et al. 2004; Suzuki et al. 2004; van der Slik et al. 2003) and reproductive success (Hiby et al. 2004; Hiby et al. 2010; Nakimuli et al. 2015).

KIR emerged comparatively recently in evolutionary history and are largely restricted to simian primates (monkeys, apes and humans) (Guethlein et al. 2015). The *KIR* gene family is diversified by both gene content variability and allelic polymorphism. However, the basic organization of the *KIR* locus is conserved amongst the catarrhine primates (Old World monkeys and apes) (Parham et al. 2010). It consists of four framework genes, which are common to all haplotypes, and a suite of homologous genes that are variably present among species and individuals (Wilson et al. 2000). A recombination site at the center of the locus defines two distinct regions: one closer to the chromosomal centromere (termed centromeric), the other closer to the chromosomal telomere (termed telomeric) (Pyo et al. 2013). Humans *KIR* haplotypes uniquely form two distinctive groups: *KIR A* haplotypes encode a fixed suite of largely inhibitory KIR whereas *KIR B* haplotypes have a variable number of inhibitory receptors and several activating receptors (Uhrberg et al. 1997).

KIR bind to the upper face of the HLA class I molecule over the C-terminal end of the bound peptide (Boyington et al. 2000; Fan et al. 2001; Liu et al. 2014). Key polymorphisms within the α_1 helix of the HLA molecule determine four major epitopes (A3/11, Bw4, C1 and C2) recognized by KIR (Saunders et al. 2015). Whereas a minority of *HLA-A* and *HLA-B* encode the A3/11 and Bw4 epitopes, all *HLA-C* have either the C1 or C2 epitope. Consequently, it is the interactions between HLA-C and the two-domain inhibitory and activating KIR that recognize HLA-C and dominate human NK cell responses (Colonna et al. 1993; Valiante et al. 1997). The two mutually exclusive HLA-C epitopes are defined by dimorphism at position 80 in the α_1 helix. The HLA-C1 epitope is defined by N80 and recognized by KIR with K44 (KIR2DL2/3, K44-KIR2DP1^F, KIR2DS2), the HLA-C2 epitope is defined by K80 and recognized by KIR with either M44 (KIR2DL1, KIR2DS1) or

T44 (KIR2DS3/5, T44-KIR2DP1^F) (Hilton et al. 2017b; Moesta et al. 2008; Moesta et al. 2010; Winter et al. 1998).

Here we review the evolution and function of human NK cell receptors that recognize HLA-C, detailing the functional consequences of their extreme diversity and the mechanisms by which they discriminate healthy cells from diseased and semi-allogeneic cells.

HLA-C evolved to be the dominant KIR ligand in humans

Human inhibitory KIR recognize four mutually exclusive epitopes on HLA class I. The KIR that recognize these epitopes comprise two lineages that have a common genetic organization amongst the catarrhine primates (Old World monkeys and apes) (Guethlein et al. 2007; Wilson et al. 2000). Lineage II KIR recognize the A3/11 and Bw4 epitopes of HLA-A and HLA-B whereas the lineage III KIR recognize the C1 and C2 epitopes of HLA-C (Moesta et al. 2008). Comparative studies examining the organization of the *KIR* and *HLA class I* loci in non-human primates have provided insight into the co-evolution of these immune system elements and contributed to our understanding of their functions in reproduction and immunity in modern humans.

Old world monkeys, such as the rhesus macaque, have counterparts to *HLA-A* and *HLA-B*, but not to *HLA-C* (Adams and Parham 2001). In this species, an abundance of *MHC-A* and *B* genes that encode the Bw4 epitope is accompanied by a corresponding expansion of the lineage II KIR that recognize them (Bimber et al. 2008; Blokhuis et al. 2010; Kruse et al. 2010). As a result, the telomeric region of the rhesus macaque *KIR* locus contains 21 *lineage II KIR* genes. By contrast, the centromeric region of the rhesus macaque *KIR* locus contains just one *lineage III KIR*, and its function is not known (Bimber and Evans 2015). The organization of the orangutan and chimpanzee *KIR* loci is the reverse. Corresponding with the emergence and fixation of *MHC-C*, the centromeric region of the *KIR* locus contains different combinations of nine *lineage III KIR* genes encoding receptors that recognize the C1 or C2 epitopes (Abi-Rached et al. 2010; Older Aguilar et al. 2010). The telomeric region has just one *lineage II KIR* encoding a receptor for Bw4-like epitopes of *MHC-A* and *MHC-B*.

In humans, the A3/11 and Bw4 epitopes are carried by a minority subset of HLA-A and HLA-B allotypes. By contrast, all HLA-C allotypes have either the C1 or C2 epitope (Parham and Moffett 2013). The result is that only ~50% of the human population have Bw4 and/or A3/11, whereas 100% have C1 and/or C2. By this simple measure, HLA-C is seen to be the dominant source of ligands for human inhibitory KIR. Together, these studies are consistent with *MHC-C* having arisen under natural selection in the higher primates to be a more specialized ligand for KIR than either HLA-A or HLA-B (Older Aguilar et al. 2010).

Contributing to the qualitative and quantitative changes in the hominid *KIR* locus was an increasing role in reproduction for interactions between *MHC-C* and *KIR*, specifically in the formation of the placenta (Moffett and Colucci 2015). Whereas HLA-A, -B and -C are co-expressed by most cells of the body, a crucial difference occurs in pregnancy, where extravillous trophoblast cells express HLA-C but not HLA-A or HLA-B (King et al. 2000). Extravillous trophoblast are cells of fetal origin that invade the mother's uterus, where they

transform the spiral arteries into large vessels, coopting sufficient maternal blood to sustain the developing fetus until the end of pregnancy (Moffett-King 2002). This invasive placental phenotype observed in hominids is absent in Old World monkeys, and thus correlates with the emergence of *MHC-C* in the orangutan.

Human-specific evolution of KIR and HLA-C

Comparing the *KIR* of different primate species shows an extraordinary degree of species-specificity that attests to their rapid evolution. This specificity is particularly evident from comparison of the human and chimpanzee *lineage III KIR*. During the speciation event that separated humans from chimpanzees ~5 million years ago, the chimpanzee line retained much of the *lineage III KIR* diversity that had evolved in the previous 10–15 million years and was present in the last common ancestor. By contrast, owing to population bottlenecks during speciation, humans retained just two *lineage III KIR*: one encoding activating *KIR2DS4* and the other encoding an inhibitory MHC-C receptor (Abi-Rached et al. 2010; Graef et al. 2009). The latter gene subsequently became subject to a process of gene duplication and differentiation that spawned a family of six human-specific *KIR* genes and formation of the distinctive *CenA* and *CenB* *KIR* haplotypes. Our recent study suggests this founder gene was *KIR2DP1^F*, the functional antecedent of the now-inactive *KIR2DP1* gene (Hilton et al. 2017a).

KIR2DP1: a human-specific relic of a once functional HLA-C receptor

KIR2DP1^F is likely to have first been a dedicated and polymorphic C1-specific receptor with K44 as the specificity determining residue (Figure 1). Subsequently, it evolved a second lineage of alleles with T44 and C2 specificity (Hilton et al. 2017a). In this way, T44 *KIR2DP1^F* served to replace the M44 *lineage III KIR* with C2-specificity that were lost from the human lineage during speciation (Abi-Rached et al. 2010; Hilton et al. 2017a). Provision of a single receptor with alternative allotypes that could recognize either the C1 or C2 epitopes was a major step forward. However, although useful as an evolutionary intermediate, *KIR2DP1^F* was subsequently usurped by K44 *KIR2DL2/3* and M44 *KIR2DL1*, dedicated high affinity receptors with specificity for the C1 and C2 epitopes of HLA-C, respectively. *KIR2DP1^F* became attenuated and subsequently inactivated due to the acquisition and propagation of a single nucleotide deletion that caused premature termination of the protein (Hilton et al. 2017a; Vilches et al. 2000). Inactivation of *KIR2DP1^F* was complete prior to the divergence of modern humans from archaic humans some 450,000 years ago (Figure 1) (Hilton et al. 2017a).

HLA-C receptors drove the functional specialization of KIR haplotypes

An early feature of human-specific evolution was the establishment of two functionally distinctive *KIR* haplotypes (Uhrberg et al. 1997). *CenA* haplotypes are characterized by strong and specific inhibitory *KIR* allotypes, whereas *CenB* haplotypes have weakened inhibitory *KIR* allotypes and a variable number of activating *KIR* (Hilton et al. 2015a). *KIR2DP1^F* allotypes contributed a key first step in this evolution. Higher affinity K44 *KIR2DP1^F* allotypes accumulated in the centromeric part of *CenA* whereas lower affinity T44 *KIR2DP1^F* allotypes, many of which also had attenuated or inactivated signaling function, accumulated in *CenB* (Hilton et al. 2017a). *KIR2DL1*, which is in strong linkage

disequilibrium with KIR2DP1 shows a similar evolutionary trajectory. Strong KIR2DL1 allotypes with high affinity for HLA-C2 and intact signaling function segregate on *CenA*, whereas weaker KIR2DL1 allotypes with reduced affinity for HLA-C2 and/or attenuated signaling function are found on *CenB* (Bari et al. 2009; Hilton et al. 2015a). The trend for inhibitory KIR with reduced capacity to recognize or respond to HLA-C2 is taken to its extreme on several truncated *CenB* haplotypes from which both *KIR2DP1* and *KIR2DL1* have been deleted (Hilton et al. 2017a; Pyo et al. 2013).

Inhibitory KIR can act to buffer imbalance in the frequencies of C1⁺ and C2⁺ HLA-C ligands

Across human populations, the frequency of *KIR B* haplotypes correlates with the frequency of HLA-C2 (Hiby et al. 2004). By extension, populations with high C2 frequency are replete with weak or inactive HLA-C2 receptor variants. This phenomenon is well illustrated by the KhoeSan of Southern Africa, a population having one of the highest known frequencies of C2 (Gonzalez-Galarza et al. 2011) who have evolved two unique KIR2DL1 allotypes, neither of which has a normal functional interaction with C2. The first of these switched its specificity from C2 to C1 and the second, although able to bind to C2, has no connection to the inhibitory signaling apparatus (Hilton et al. 2015b). In analogous fashion, attenuated or inactivated C1-receptors are found in populations with high frequencies of HLA-C1. As an example, the Yucpa Amerindians, who have an unusually high frequency of C1⁺HLA-C*07:02 evolved two KIR2DL3 variants, one with attenuated binding of C1 and the other that cannot bind C1 (Gendzekhadze et al. 2009). Thus, inhibitory lineage III KIR appear to act as a buffer that respond to changes in HLA-C frequency. It is likely that this mechanism acts to maintain appropriate NK cell function, despite changes in HLA-C epitope frequency. That the binding affinity, cell-surface expression and signaling capacity of human inhibitory HLA-C receptors appear malleable (Table 1), indicates they are well-suited to this purpose.

KIR peptide selectivity plays a role in NK-mediated recognition of altered self

NK cells and CD8 T cells play complementary roles in the cellular immune response. Whereas CD8 T lymphocytes kill cells presenting particular non-self peptides bound by HLA class I, NK cells kill cells with a deficiency of surface HLA class I. Reflecting these different roles, the T-cell receptor (TCR), the antigen receptor of CD8 T-cells, is exquisitely sensitive to changes in the bound peptide repertoire (Garcia and Adams 2005). By contrast, KIR, the major variable receptors of NK cells, are less finely tuned, being able to recognize a broader range of peptide-HLA combinations (Boyington and Sun 2002). Despite the broader specificity, pioneering studies in this field suggested that patterns of NK-cell mediated cytotoxicity were influenced by the nature of the peptide bound to HLA class I (Malnati et al. 1995; Peruzzi et al. 1996; Storkus et al. 1992). Although KIR are not peptide specific like the TCR, there is considerable evidence that they exhibit a sophisticated peptide selectivity. There is now an increasing body of work exploring its extent and functional consequences (Table 2).

KIR peptide selectivity was first suggested by studies in which mutations within the peptide binding cleft of HLA class I were sufficient to change the cytotoxic response of NK cell clones to target cells (Malnati et al. 1995; Peruzzi et al. 1996). Subsequent studies using amino-acid substituted peptide variants showed how specific peptides could modulate

KIR2DL1 and KIR2DL2 recognition of HLA-C (Boyington et al. 2000; Rajagopalan and Long 1997; Zappacosta et al. 1997). These studies highlighted the formative roles for the amino acid residues at P7 and P8 of the bound peptide. Large, negatively charged amino acids reduced or abrogated KIR binding and exposed target cells to NK-cell mediated lysis. The structural basis for this selectivity became clear from the crystallographic structure of the KIR2DL2/HLA-C*03:04 complex, which showed how KIR2DL2 binds over the C-terminal part of the bound peptide, making direct contacts with residues P7 and P8 (Boyington et al. 2000). The structures of KIR2DS2 bound to HLA-A*11:01 and KIR2DL1 bound to HLA-C*04:01 show broadly similar binding modes, though they exhibit subtle differences in peptide accommodation (Fan et al. 2001; Liu et al. 2014). Unlike KIR2DL2 and 2DS2, KIR2DL1 does not make any direct contact with bound peptide, despite its demonstrated sensitivity to mutation at P8 (Fan et al. 2001; Rajagopalan and Long 1997).

A hierarchy of peptide selectivity among inhibitory HLA-C receptors

Recent studies point to differences in peptide selectivity within the various inhibitory KIR that recognize HLA-C (Cassidy et al. 2015; Sim et al. 2017). Consistent with the structural picture, KIR2DL2/3 shows greater peptide selectivity than KIR2DL1 (Sim et al. 2017). Supporting this finding, our examination of endogenously processed peptides from C1⁺HLA-C and HLA-B showed that <25% of the peptides are strong KIR2DL3 ligands (Hilton et al. 2017b). The peptide selectivity of KIR2DL2/3 was further highlighted by the observation that peptide positions other than P7 and P8 have potential to influence the recognition of C1⁺HLA-C (Hilton et al. 2017b; Sim et al. 2017). That KIR2DL3 appears as the receptor with the most peptide selectivity provides a compelling rationale for the observation that KIR2DL3 binding to C1⁺HLA-C is weaker than KIR2DL1 binding to C2⁺HLA-C (Moesta et al. 2008). These studies show that KIR display peptide selectivity, but retain the capacity to bind a range of different peptide-HLA combinations.

Peptide antagonism allows NK cells to respond to subtle changes in peptide repertoire

Studies examining the KIR reactivity of single peptide-HLA complexes were crucial in establishing the peptide selectivity of KIR binding. However, they were not designed to inform how a mixture of competing peptides, as occurs *in vivo*, acts to modulate NK cell reactivity. Experiments to compare the effects of peptides that bind weakly or strongly to the same HLA-C allotype are now addressing this question. A key discovery from such studies was that some weak KIR ligands compete effectively with strong KIR ligands. This phenomenon is termed *peptide antagonism* (Cassidy et al. 2015; Fadda et al. 2010). Such competition reduces KIR-mediated inhibition (Borhis et al. 2013; Fadda et al. 2010) to favor target cell lysis. This provides an alternative mechanism by which the innate immune system can respond to changes in the peptide repertoire bound by HLA-C. Peptide antagonism is hypothesized to be important during viral infection when subtle changes in the peptide repertoire occur in the absence of HLA class I down-regulation (Fadda et al. 2010).

Peptide selectivity permits viruses to subvert NK-cell mediated immunity

During a viral infection, interactions between KIR and HLA-C allow NK cells to mount an effective immune response in complementary ways. Down-regulation of HLA-C triggers cytotoxicity by a missing-self response, whereas presentation of viral peptide antigens that

are weak KIR ligands triggers cytotoxicity through peptide antagonism (Figure 2). To this extent, KIR peptide selectivity can be advantageous to the host in responding to viral infection.

Conversely, viral peptides that form strong ligands for inhibitory KIR may undermine the immune response by preventing NK-cell mediated killing of infected cells (Figure 2). Such “escape mutants” were first proposed by *Alter et al.*, who found that new mutations in the HIV-1 sequence enhanced the binding of KIR2DL2 to HIV-1 infected CD4⁺ T-cells (Alter et al. 2011). This enhanced binding correlated with reduced antiviral activity of NK cells and suggested that direct NK-cell mediated immune pressure on HIV-1 had selected for the new mutations. A peptide derived from the variant HIV-1 p24 Gag epitope reduces the cytotoxicity mediated by KIR2DL3⁺NK cells, providing direct evidence for selection of a Gag peptide that prevents NK-cell response to HIV-infected cells (Holzemer et al. 2015; van Teijlingen et al. 2014). This Gag-derived variant epitope is well expressed by HLA-C*03:04 and enhances binding of KIR2DL3, probably because of the T for V substitution at P8 of the variant peptide (Holzemer et al. 2015).

Taken together, it is clear that KIR bind numerous peptide-HLA combinations, but also retain a degree of peptide selectivity that has functional consequences for NK-cell mediated innate immunity. Further, the degree of KIR peptide selectivity appears finely balanced: high selectivity promotes strong immunity through peptide antagonism but also allows a rapidly-evolving virus to escape detection by production of strong inhibitory peptide. Low KIR peptide selectively reduces the potential for peptide antagonism but also makes viral escape less likely. Despite the recent advances, further investigation will be needed to understand how KIR respond to the complex peptide repertoires that result from HLA class I polymorphism, viral infection and malignant transformation.

Activating HLA-C receptors: attenuated relics or sensitive sensors of “altered self”?

Two lines of evidence have suggested that the activating lineage III KIR recognize epitopes of HLA class I. One is their extensive sequence homology with the inhibitory lineage III KIR that recognize HLA-C (Abi-Rached and Parham 2005); the other is the large number of epidemiologic studies that have correlated activating lineage III KIR and their putative ligands with a spectrum of infectious, auto-immune and reproductive diseases (summarized in Table 3). Despite these implications, ligands for the five activating lineage III KIR have, in general, been harder to identify than those for their inhibitory counterparts. Contributing to this relatively slow progress is their overall lower affinity for HLA class I (Graef et al. 2009; Hilton et al. 2012; Hilton et al. 2015a; Moesta et al. 2010; Older Aguilar et al. 2011; Stewart et al. 2005), a narrower specificity for HLA class I and an increased peptide selectivity (Graef et al. 2009; Liu et al. 2014; Stewart et al. 2005). A further obstacle has been a dearth of cellular assays that can be used to probe the binding specificity of activating KIR on NK cells, and the functional response they produce. A reporter system, in which signaling through a modified activating KIR produces intracellular expression of a fluorescent protein, is an approach with potential to solve this problem (van der Ploeg et al. 2017).

KIR2DS1 recognition of HLA-C2 targets has been shown in a number of experimental systems and it is the activating KIR for which the ligand specificity is most clearly defined (Table 4) (Hilton et al. 2015a; Moesta et al. 2010; Pende et al. 2009; Stewart et al. 2005; van der Ploeg et al. 2017). KIR2DS1 has an affinity for C2 that is significantly lower (~50%) than that of inhibitory KIR2DL1 (Hilton et al. 2012; Hilton et al. 2015a; Moesta et al. 2010). This reduced avidity stems largely from the threonine to lysine mutation at position 70, in the D1 domain (Hilton et al. 2012). In contrast, the presence at position 45 of tyrosine in KIR2DS2 and phenylalanine in KIR2DL2, reduces the avidity of KIR2DS2 for C1⁺HLA-C to a barely detectable level (Moesta et al. 2010; Saulquin et al. 2003; Winter et al. 1998). This low avidity may be compounded by the considerable peptide selectivity of KIR2DS2, which is apparent from the structural analysis of KIR2DS2 bound to HLA-A*11:01 (Liu et al. 2014). KIR2DS4 also recognizes HLA-A*11:02 in a peptide dependent way (Graef et al. 2009), the result of a proline 71, valine 72 motif, which was introduced into KIR2DS4 by gene conversion with KIR3DL2 prior to the divergence of humans from chimpanzees (Graef et al. 2009).

Recognition of altered HLA targets by activating KIR

The reported peptide selectivity of activating KIR may enable NK cells to eliminate infected cells through recognition of viral peptides bound by HLA class I. Supporting this hypothesis, KIR2DS1 has been shown to recognize a viral-induced ligand on CMV infected HLA-C2⁺ human fibroblasts (van der Ploeg et al. 2017). However, the mechanistic basis for this recognition is not fully understood and could result from changes in HLA-C glycosylation, co-presentation of HLA-C with a viral ligand or recognition of HLA-C open conformers that lack associated peptide or β_2 -microglobulin (van der Ploeg et al. 2017). Several activating KIR, including KIR2DS4, have been shown to recognize an open conformer of the non-classical HLA-F (Goodridge et al. 2013). A similar mechanism may underlie the recent observation that KIR2DS2 recognizes cancer cell lines in a β_2 -microglobulin independent fashion (Thiruchelvam-Kyle et al. 2017). The direct recognition of virally-induced ligands by activating NK cell receptors has been observed in mice (Arase et al. 2002; Smith et al. 2002), but is yet to be confirmed in the human system. Together, these studies suggest that activating KIR recognize altered forms of HLA class I that may be up-regulated during viral infection or malignant transformation.

A role for activating KIR in regulating placentation

Activating KIR are expressed and appear functional on uterine NK cells (Hiby et al. 2010; Kennedy et al. 2016; Xiong et al. 2013). Further, epidemiologic studies are consistent with the activating KIR playing a role in placental development (Hiby et al. 2004; Hiby et al. 2010; Hiby et al. 2014; Nakimuli et al. 2015). The genes of the telomeric *KIR B* haplotype (*TeIB*) have consistently been associated with protection against the development of pre-eclampsia and other disorders of pregnancy that result from insufficient invasion by extravillous trophoblast (Hiby et al. 2004; Hiby et al. 2010; Nakimuli et al. 2015). This protective effect is more marked in pregnancies where the fetus expresses HLA-C2, suggesting that a C2-specific KIR encoded by *TeIB* mediates the protection. In women of European ancestry this KIR is KIR2DS1 (Hiby et al. 2010), whereas in women of African ancestry it is KIR2DS5 (Nakimuli et al. 2015). Previously not known to bind any HLA class

I ligand, the protective *006 allotype of KIR2DS5 has recently been shown to bind weakly to C2⁺HLA-C (Blokhuys et al 2017, submitted). By contrast, KIR2DS5*002, which showed no correlation with protection, does not bind to any HLA class I. This result highlights the extent to which allelic the polymorphism of an activating KIR can contribute different ligand binding properties. Although considerably less polymorphic than the inhibitory lineage III KIR, similar changes in binding affinity have been observed for KIR2DS1 allotypes (Hilton et al. 2015a). The extent to which peptide selectivity of activating KIR is important in the context of reproduction has yet to be determined. However, given that HLA-C expressed on extravillous trophoblast may sample a unique proteome, further studies of its effect are warranted.

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Figure 1. Evolution of human inhibitory lineage III KIR

The evolution of human-specific inhibitory *lineage III KIR* of the centromeric *KIR* haplotype during the last five million years. For each *KIR* gene the residue encoded at position 44 is given in yellow. *CenA* associated allotypes are shown in blue and *CenB* associated allotypes are shown in orange.

(I) *KIR2DP1^F* was the ancestral inhibitory lineage III KIR with K44 and C1 specificity

(II) *KIR2DP1^F* evolved a second lineage with T44 and C2 specificity

(III) Evolution of C1 specific *KIR2DL2/3* with K44 and of C2 specific *KIR2DL1* with M44

(IV) Functional specialization of *KIR2DL2/3* and *KIR2DL1*. *CenA* haplotypes have attenuated C1 specific *KIR2DL3* and strong C2 specific *KIR2DL1*. *CenB* haplotypes have strong C1 specific *KIR2DL2* allotypes and attenuated C2 specific *KIR2DL1*. *KIR2DP1^F* and *KIR2DL1* are deleted from selected *CenB* haplotypes.

(V) Before the separation of archaic humans from modern humans, *KIR2DP1^F* became inactivated to form *KIR2DP1*.

Figure 2. HLA-C receptor peptide selectivity modulates NK-cell mediated immunity during viral infection

(A) Self peptides (green) bound by HLA-C and expressed on healthy target cells provide strong ligands for inhibitory KIR, preventing NK-cell mediated lysis.

(B) During viral infection, down-regulation of HLA class I results in NK cell activation and target cell lysis caused by the loss of KIR mediated inhibition (upper panel). Presentation of viral peptides that form weak ligands for inhibitory KIR (pink) antagonize inhibition of strong KIR ligands (green) resulting in NK cell activation and target cell lysis (center panel). Presentation of viral peptides that are strong ligands for inhibitory KIR (yellow) allow the virus to escape from NK-cell mediated anti-viral immunity.

Inhibitory human HLA-C receptor loss of function variants

Table 1

Listed are inhibitory lineage III KIR that have lost the ability to induce an inhibitory response through engagement with their cognate HLA class I ligands. For each KIR are listed the names of the inactivated allotype, the mutation that causes the inactivation and the mechanism of inactivation.

KIR	Allele	Mutation	Mechanism of inactivation	Reference
KIR2DL1	*013N	E35Ter	Truncated protein	Hou et al. (2010)
	*014	G179S	Misfolded protein and intracellular retention	Hilton et al. (2015)
	*022	M44K	Specificity change to bind C1*HLA-C	Hilton et al. (2015)
	*026	W246Ter	Truncated protein with loss of intracellular signaling domain	Hilton et al. (2015)
KIR2DL2	*004	H41T	Misfolded protein and intracellular retention	VandenBussche et al. (2006)
KIR2DL3	*008N	Ins86/Ter124	Truncated protein	Gendzekhadze et al. (2009)
KIR2DP1	All	Del88/Ter124	Truncated protein	Vilches et al. (2000)

Table 2
Peptide selectivity of inhibitory human HLA-C receptors

Listed are the inhibitory lineage III KIR that display peptide selectivity in their recognition of HLA class I. For each study is listed we give the KIR and HLA-C allotypes examined and the major findings.

Theme	KIR	HLA class I	Major findings	Reference
Peptide selectivity	KIR2DL2/3	HLA-C*03:04	Bound peptide required for protection from cytotoxicity; Several peptides protect cells from lysis; Range of protection seen with different peptides	Zappacosta et al. (1997)
	KIR2DL1	HLA-C*04:01	KIR2DL1 recognition of HLA-C*04 is peptide dependent; Large, negatively charged residues at P7 and P8 abrogate KIR binding	Rajagopalan and Long (1997)
	KIR2DL2	HLA-C*03:04	Direct contact between KIR2DL2 and P7/P8 of GAVDPLLAL; Mutation at P8 to Y or K prevents KIR binding	Boyington et al. (2000)
	KIR2DL1	HLA-C*04:01	No direct contact of KIR2DL1 to bound peptide	Fan et al. (2001)
	KIR2DS1 KIR2DS2 KIR2DL1 KIR2DL2 KIR2DL3	HLA-C*03:04 HLA-C*04:01	Mutation at peptide P8 has the major influence on activating and inhibitory KIR binding; P7 shows a weaker effect	Stewart et al. (2005)
	KIR2DL1 KIR2DL2 KIR2DL3	HLA-C*05:01 HLA-C*08:02	KIR2DL2/3 has greater peptide selectivity than KIR2DL1; Cross reactive KIR show higher peptide selectivity; Specific peptides allow KIR2DL1 to bind C1 ⁺ HLA-C	Sim et al. (2017)
	KIR2DL3	HLA-C*01:02 HLA-B*46:01	<25% of endogenously processed peptides form strong ligands for KIR2DL3	Hilton et al. (2017)
Peptide antagonism	KIR2DL2 KIR2DL3	HLA-C*01:02	C*01:02 bound peptides form strong, weak and null ligands for KIR2DL2 and KIR2DL3; Weak binding peptides antagonize strong peptides	Fadda et al. (2010)
	KIR2DL3	HLA-C*01:02	Antagonistic peptides prevent tight clustering of KIR2DL3 at the immune synapse; Prevents SHP-1 recruitment and signaling	Borhis et al. (2013)
	KIR2DL2 KIR2DL3	HLA-C*01:02	KIR2DL3 is more sensitive to peptide antagonism than KIR2DL2	Cassidy et al. (2015)
Viral evasion	KIR2DL2	HLA-C*03:04	HIV-1 sequence polymorphisms enhance binding to KIR2DL2	Alter et al. (2011)
	KIR2DL2	HLA-C*03:04	3 HIV-1 Gag epitopes reduce KIR2DL2 binding and inhibition	van Teijlingen et al. (2014)
	KIR2DL3	HLA-C*03:04	p24 Gag epitope reduces KIR2DL3 binding and inhibition	Holzemer et al. (2015)

Table 3

Associations of activating HLA-C receptors with human disease

Listed for each activating KIR is the autoimmune, infectious or reproductive disease with which it has been associated, as well as the major findings of the study. Cognate HLA class I ligands are listed where reported.

Theme	KIR	HLA class I	Disease	Major findings	Reference
Autoimmunity	2DS1	–	Psoriasis vulgaris	2DS1 predisposes to disease	Suzuki et al. (2004)
	2DS1	HLA-C*06:02	Psoriasis vulgaris	2DS1 + HLA-C*06 predisposes to disease	Luszeck et al. (2004)
	2DS1	HLA-C*06:02	Psoriasis vulgaris	2DS1 + HLA-C*06 predisposes to disease	Jobim et al. (2008)
	2DS1	HLA-C*06:02	Guttate psoriasis	2DS1 + HLA-C*06 predisposes to disease	Holm et al. (2005)
	2DS1 and 2DS2	–	Psoriatic arthritis	2DS1 and 2DS2, no inhibitory KIR ligands predispose	Martin et al. (2002)
	2DS1	HLA-C*06:02	Psoriatic arthritis	2DS1 + HLA-C*06 predisposes to disease	Williams et al. (2005)
	2DS2	–	Psoriatic arthritis	2DS2 predisposes to disease	Chandran et al. (2014)
	2DS1	HLA-C2	Multiple sclerosis	2DS1 protective, effect stronger with C2	Fusco et al. (2010)
	2DS1	–	Multiple sclerosis	2DS1 protective against disease	Bettencourt et al. (2014)
	2DS2	–	Rheumatoid arthritis	Increased frequency of 2DS2 on NK and T cells in patients with vasculitis	Yen et al. (2001)
	2DS2 and 2DL2	–	Rheumatoid arthritis	2DS2 and 2DL2 predispose to disease	Ramirez-de los Santos et al. (2012)
	2DS2	–	Scleroderma	2DS2 and lack of 2DL2 predispose to disease	Momot et al. (2004)
	2DS2	–	Scleroderma	2DS2 and lack of 2DL2 predispose to disease	Salim et al. (2010)
	2DS1	–	Systemic lupus erythematosus	2DS1 and lack of 2DS2 predisposes to disease	Pellet et al. (2007)
	2DS1 and 2DL2	–	Systemic lupus erythematosus	2DS1 and 2DL2 predispose to disease	Hou et al. (2010)
	2DS1	HLA-C2	Systemic lupus erythematosus	2DS1 + HLA-C2 predisposes to disease	Hou et al. (2015)
	2DS1	HLA-C2	Ankylosing spondylitis	2DS1 + HLA-C2 predisposes to disease	Jiao et al. (2008)
	2DS1 and 3DS1	–	Ankylosing spondylitis	2DS1 and 3DS1 predispose to disease	Diaz-Pena et al. (2015)
	2DS5	HLA-C1	Ankylosing spondylitis	2DS5 + HLA-C1 protective	Nowak et al. (2015)
	2DS2	HLA-C1	Type 1 diabetes	2DS2 + HLA-C1 predisposes to disease	Van der Sliik et al. (2003)
	2DS2 and 2DL2	–	Type 1 diabetes	2DS2 and 2DL2 predispose to disease	Nikitina-Zake et al. (2004)
	2DS2 and 2DL2	–	Immune Thrombocytopenia	2DS2 and 2DL2 predispose to disease	Nourse et al. (2012)
	2DS3 and 2DS5	–	Immune Thrombocytopenia	2DS3 predisposes, 2DS5 protects against disease	Seymour et al. (2014)
	2DS1	–	Atopic dermatitis	2DS1 protects against disease	Niepieklo-Miniowska et al. (2013)
	2DS1	HLA-C2	Autoimmune hepatitis	2DS1 and C2 predisposes to disease	Littera et al. (2016)
	2DS2	HLA-C1	Hashimoto's thyroiditis	2DS2 + HLA-C1 predisposes to disease	Li et al. (2016)

Theme	KIR	HLA class I	Disease	Major findings	Reference
Infection	2DS3	–	Microscopic polyangitis	2DS3 predisposes to disease	Miyashita et al. (2006)
	2DS3	–	Vogt-Koyanagi-Harada disease	2DS3 predisposes to disease	Sheereen et al. (2011)
	2DS1	HLA-C2	Kaposi's sarcoma	2DS1 + HLA-C2 predisposes to disease	Guerini et al. (2012)
	2DS1	HLA-C2	Ocular toxoplasmosis	2DS1 + HLA-C2 predisposes to disease	Ayo et al. (2016)
	2DS1	–	Sepsis	2DS1 reduced in patients	Oliveira et al. (2017)
	2DS1	HLA-C2	HIV	2DS1 + certain HLA-C2 allotypes associated with elite controller status	Malnati et al. (2017)
	2DS1 and 2DS3	–	Ebola virus	2DS1 and 2DS3 associated with fatal outcome	Wauquier et al. (2010)
	2DS1, 2DS3 and 3DS1	–	Pulmonary tuberculosis	2DS1, 2DS3 and 3DS1 predispose to disease	Lu et al. (2012)
	2DS1 and 2DS5	–	Pulmonary tuberculosis	2DS1 and 2DS5 predispose to disease	Pydi et al. (2013)
	2DS1 and 2DS5	HLA-C2	Dengue fever	2DS1, 2DS5 and 2DS1 w/C2 confer protection	Beltrame et al. (2013)
	2DS1 and 3DS1	–	EBV/Hodgkin's lymphoma	2DS1 and 3DS1 protect against disease	Besson et al. (2007)
	2DS1 and 3DS1	–	HPV/Respiratory papillomatosis	2DS1 and 3DS1 protect against disease	Bonagura et al. (2010)
	2DS1, 2DS2 and 3DS1	–	Leprosy	2DS1, 2DS2 and 3DS1 protect against disease	Jarduli et al. (2014)
	2DS2 and 2DL2	–	HSV-1	Lack of 2DS2 and 2DL2 confers resistance	Estefania et al. (2007)
	2DS2 and 2DL2	HLA-C1	Chagas disease	Presence of 2DS2 + C1, no 2DL2 predisposes to chronic disease	Ayo et al. (2015)
Reproduction	2DS5 and 3DS1	–	H1N1 Influenza	2DS3 and 3DS1 predispose to severe disease	Aranda-Romo et al. (2012)
	2DS1	–	Recurrent miscarriage	Lack of 2DS1 predisposes to disease	Hiby et al. (2008)
	2DS1	HLA-C2	Pre-eclampsia	2DS1 + HLA-C2 protective	Hiby et al. (2010)
	2DS5	HLA-C2	Pre-eclampsia	2DS5 variants + HLA-C2 protective	Nakimuli et al. (2015)
	2DS5	HLA-C2	Endometriosis	2DS5 + HLA-C2 protective	Nowak et al. (2015)

Table 4
Direct binding of activating lineage III KIR to HLA class I and other ligands

Listed are the known ligands for the activating lineage III KIR. For each KIR is shown the HLA class I target, where known, and the major findings of the study reported.

KIR	HLA class I	Major findings	Reference
2DS1	HLA-C*04:01 HLA-C*06:02	2DS1 tetramers recognize C2 ⁺ HLA-C; recognition sensitive to mutation at peptide positions P7 and P8	Stewart et al. (2005)
	HLA-C*04:01 HLA-C*05:01 HLA-C*06:02	Direct binding of 2DS1 to C2 on leukemic blasts and 2DS1 mediated killing	Pende et al. (2009)
	7 C2 ⁺ HLA-C	KIR2DS1 binding to seven C2 ⁺ HLA-C allotypes	Moesta et al. (2010)
	7 C2 ⁺ HLA-C	KIR2DS1 allotypes show variable avidity for C2 ⁺ HLA-C allotypes	Hilton et al. (2015)
	C2 ⁺ fibroblasts	KIR2DS1 recognizes C2 ⁺ CMV infected fibroblasts	Van der Ploeg et al. (2017)
2DS2	HLA-C*03:02	Weak, peptide specific binding of 2DS2 tetramer to C1 ⁺ HLA-C*03:02	Stewart et al. (2005)
	HLA-C*16:01	Weak binding of 2DS2-Fc to C1 ⁺ HLA-C*16:01	Moesta et al. (2010)
	HLA-A*11:01	Direct binding of 2DS2 to A*11:01 in a peptide specific mode; Binding sensitive to mutations at peptide P8	Liu et al. (2014)
	Unknown	Direct binding of 2DS2 to cancer cells lines in β_2 M independent manner	Thiruchelvam-Kyle et al. (2014)
2DS4	HLA-A*11:02	KIR2DS4 binds to HLA-A*11 and shows weak binding to selected C1 ⁺ HLA-C and C2 ⁺ HLA-C allotypes	Graef et al. (2009)
2DS4	HLA-F	KIR2DS4 binds open conformer of HLA-F	Goodridge et al. (2013)
2DS5	7 C2 ⁺ HLA-C	Weak binding of selected 2DS5 allotypes to C2 ⁺ HLA-C	Blokhuis et al. (2017)