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The Yin-Yang of KIR3DL1/S1: Molecular Mechanisms and Cellular Function

Geraldine M O'Connor and **Daniel W McVicar**

Cancer and Inflammation Program, National Cancer Institute at Frederick, NIH, Frederick, MD 21702, USA

Abstract

Killer Immunoglobulin-like Receptors (KIR) are a family of receptors expressed on Natural Killer (NK) and T cell subsets. KIR3DL1 is a highly polymorphic receptor that binds to groups of HLA-A and HLA-B allotypes that express the Bw4 epitope. The variation in KIR3DL1 allotypes manifests at a number of levels. Most dramatically, a common allelic variant encodes an activating rather than an inhibitory receptor (KIR3DS1). In addition, sequence variants can affect both the frequency of expression within the NK cell population, and the intensity of expression on a given cell. KIR3DL1 polymorphism also influences the interaction with HLA-Bw4 molecules due to contacts with the HLA molecule itself and sensitivity to the presented peptide. There is a body of evidence from genetic association studies supporting the biological significance not only of the interaction of KIR3DL1 with HLA-Bw4, but also the functional variation seen with different KIR3DL1 and HLA allotypes. In this review we will discuss our current understanding of KIR3DL1 function and our recent insights from the structure of the KIR3DL1 in complex with HLA. In addition, we will summarize our current understanding of KIR3DS1, including its ligand specificity and role in immune responses.

Keywords

Killer Immunoglobulin-like Receptors; Natural Killer Cells; Human Leukocyte Antigen; Innate Immunity

I. Introduction

In traditional Chinese philosophy and medicine, the concept of yin-yang is used to describe how seemingly opposite forces are, in fact, interconnected and interdependent. Although the most familiar representation of the philosophy in the western world is the Taijitu symbol of stark contrast between light and dark, yin and yang are actually complementary, not opposing, forces, interacting to form a whole greater than either separate part. A wonderful example of this concept in biology comes from the vast array of immune regulatory receptors, some inhibitory and some activating, which work in concert to coordinate the escalation of an effective immune response upon infection, while sparing bystander tissues from collateral damage and mediating an effective drawdown once the danger has been cleared. Several receptor systems achieve this balance through multiple related loci with various functional capabilities, but the Killer Immunoglobulin-like Receptors (KIR) provide a unique perspective, with alleles of the same locus displaying apparently opposite biochemical function, as found in the KIR3DL1/S1 locus.

Corresponding Author: Daniel W. McVicar, NCI-Frederick, Bldg 560 Rm 31-50, Frederick, MD 21702, Tel: 301 846 5163, Fax: 301 846 1673.

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The KIR are a family of receptors expressed on Natural Killer (NK) and T cell subsets.[1] Members include KIR3DL1, 2, 3, KIR3DS1, KIR2DL1, 2, 3, 4, 5A, 5B and KIR2DS1, 2, 3, 4, 5 as well as the pseudogenes 2DP1 and 3DP1. These receptors are characterized by the presence of either two (2D) or three (3D) extracellular Ig domains. The functional nature of these receptors are dictated by the transmembrane and cytoplasmic domains; inhibitory receptors have long (L) cytoplasmic tails containing Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIMs), while activating receptors have short (S) cytoplasmic tails and couple to the activating adaptor DAP12 via a charged residue in the transmembrane domain. The exception to this is KIR2DL4, which despite a long cytoplasmic tail with an ITIM, transduces a positive signal via its interaction with the activating adaptor $Fc_eR1\gamma$.[2, 3] The best-described ligands for the KIR (primarily inhibitory KIR) are groups of HLA molecules. Although the function of the activating KIR is not well understood, inhibitory KIR are known to play a role in the maintenance of NK cell tolerance to self, and in the generation of mature, fully functional NK cells through a process of NK cell licensing. In this review, we will examine the evidence for the functional role of KIR3DL1 polymorphism, including its Yang counterpart KIR3DS1, explore the role of HLA and peptide variation in KIR3DL1-ligand interactions, and review KIR3DL1 functions in both health and disease.

II. Function of KIR3DL1

KIR3DL1 is one of the most highly polymorphic members of the KIR family.[4] As its name suggests this type I transmembrane receptor contains three extracellular Ig domains, termed D0 (membrane distal), D1 and D2 (membrane proximal). The D0 domain is a feature of 3D KIR and of type II 2D KIR (KIR2DL4, 2DL5, which contain a D0 and a D2 domain), while type I 2D KIR have a D1–D2 configuration. The cytoplasmic domain of KIR3DL1 contains two ITIM motifs (I/VxYxxL) that mediate its inhibitory function. Receptor engagement leads to phosphorylation of the ITIMs by members of the Src family kinases and the subsequent recruitment of protein tyrosine phosphatases SHP-1 and SHP-2.[5] These phosphatases are believed to inhibit NK cell activity by the dephosphorylation of key substrates (including Vav-1, ZAP70, PLC-γ and LAT) activated by the engagement of activating NK cell receptors. Engagement of inhibitory KIR leads to an inhibition of NK cell mediated cell cytotoxicity and cytokine production.[6] The cytoplasmic tail of KIR3DL1 also contains targets for serine/threonine kinases, which influence the level of KIR3DL1 surface expression via control of receptor internalization, turnover and recycling.[7, 8] In contrast, engagement of activating KIR leads to signaling downstream of DAP12, including activation of PLC-γ1, Syk/ZAP70, MAP kinases and calcium mobilization.[9] This in turn leads to activation of NK cell cytotoxicity and IFN-γ production.

KIR3DL1 expression on NK cells is expected to inhibit the lysis of target cells bearing its HLA-Bw4 ligand at steady state. The loss of this inhibitory signal, through the loss or alteration of class I expression during infection or transformation, would then lead to the activation of NK cells that depend on KIR3DL1 engagement to prevent their activation. As a consequence, NK cell-mediated killing would eliminate the affected target and the NK cell would produce pro-inflammatory cytokines including IFN-γ to rally the subsequent immune response. In addition to this role in mature NK cells, the KIR3DL1-HLA interaction is involved in the process by which developing NK cells acquire full functional capacity, in a process termed licensing or education. Current models suggest that as NK cells develop, they acquire a variety of HLA specific receptors in a random, variegated fashion, largely independent of the presence of the corresponding HLA ligands. Thus the potential arises for NK cells to develop that lack any receptor that would prevent self-recognition and activation. While we have come to appreciate that these NK cell subsets do exist, they are hyporesponsive (in the absence of cytokine stimulation).[10] Accordingly, studies have shown

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that in donors expressing HLA-Bw4, a greater portion of KIR3DL1+ NK cells are fully functionally competent than NK cells that lack KIR3DL1 expression.[11, 12]

In addition to their expression on NK cells, KIR are also expressed on generally small portions of T cell populations including γδ T cells, $CD4^+$ T cells and $CD8^+$ T cells. Although the function of KIR on T cells is much less well understood, it has been reported that KIR ligation can inhibit the cytolytic ability, cytokine production and proliferation of T cells.[13, 14, 15] In addition to this inhibition of effector function, KIR3DL1 expression on T cells can protect these cells from activation-induced cell death following stimulation, at least in part by preventing the up-regulation of Fas ligand.[16] These findings raise the possibility that preservation of T cell populations under inflammatory conditions may be a key role for KIR although clearly much more work on the regulation of T cells by KIR is needed.

III. The role of KIR3DL1 polymorphism

One of the hallmarks of KIR family members is the very high degree of sequence variation seen across individuals. KIR3DL1 is particularly highly polymorphic, with more than 70 alleles described to date.[17] Individual alleles are identified by their suffix number (e.g. KIR3DL1*001). Unique among the *KIR* loci, one of the common *KIR3DL1* alleles encodes an activating rather than an inhibitory receptor termed KIR3DS1. This receptor will be discussed in detail later.

Analysis of sequences of many *KIR3DL1* alleles led Norman *et al.* to group all alleles into one of three families: *3DS1-like*, *3DL1*005-like* and *3DL1*015-like.*[18] Statistical analysis suggests these three lineages have been maintained through balancing selection for more than 3 million years of human evolution, implying biological significance of the familial separation. In contrast to the lineage encoding the activating *KIR3DS1*, which is dominated by a single allele (*KIR3DS1*013*), there is great diversity in each of the two inhibitory lineages. At a protein level, this diversity comes from residues in both the D0 domain of the protein and the D1–D2 domains, two regions that play distinct roles in interaction with ligand (see below). Remarkably, it appears that the variation at several of these positions has been maintained under positive selection throughout evolution, suggesting important functional roles for these polymorphisms.

One of the first experimental observations to firmly suggest that KIR3DL1 allelic polymorphism influences function came from the systematic staining of NK cells of multiple donors with the anti-KIR3DL1 antibody DX9.[19] The staining pattern of donors fell into four distinct categories; none, low intensity, high intensity or bimodal patterns of staining. Gardiner *et al.* showed that this correlated with the presence of different allotypic variants of KIR3DL1. Expression of KIR3DS1 or 3DL1*004 resulted in no DX9 reactivity, allotypes such as *005 resulted in dim staining and others such as *001 and *015 gave high intensity peaks; bimodal patterns were seen in heterozygous donors. While KIR3DS1 is simply not recognized by the DX9 clone, the pattern seen with other KIR3DL1 allotypes is a direct reflection of the level of cell surface expression rather than differences in affinity for the antibody.[18] Since this observation, several polymorphic amino acids (including 75, 82 and 186) have since been identified which directly modulate the amount of KIR3DL1 found at the NK cell surface.[20, 21] The most extreme example is the presence of both L82 and S186 in KIR3DL1*004 resulting in a protein that is completely retained intracellularly.[20, 22] In addition to the intensity at which individual KIR3DL1 allotypes are expressed, the percentage of NK cells which express a given KIR3DL1 allotype also varies with highly expressed allotypes often also present on a higher frequency of NK cells (see below).[23]

While some of the KIR3DL1 sequence variants result in modulation of the amount of receptor at the cell surface, what role do the remaining polymorphisms play? The control of

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ligand/receptor interactions was an obvious possibility deserving investigation. Although structure-based molecular dissection of binding is now underway (see below) the role of KIR3DL1 sequence variation in ligand interaction was initially explored by examining the functional response of different KIR3DL1 allotypes upon interaction with a panel of single HLA class I expressing target cells. Indeed, these studies uncovered a role of polymorphic KIR3DL1 residues in dictating the strength of interaction with HLA molecules.[24, 25] In a comparison of 3DL1*002 or 3DL1*007 expressing cell lines and their interaction with HLA-B*2705, Carr *et al.* determined that position 238 in the D2 domain and 320 in the transmembrane domain are both involved in the stronger functional response of 3DL1*002 relative to *007. In a subsequent comparison of the interaction with B*5801 by Yawata *et al.*, *007 was again found to be a weak inhibitor with a defined hierarchy of 3DL1*007 < *020 < *015 < *005 < *001.[23] As informative as these reports are, they are limited by the use of individual target cell populations and it is unclear from this work if there is any impact of the relative levels of receptor expression in these assays. Additional work that accounts for the differing frequencies, peptide specificities and levels of expression on individual cells may be required to fully explain the relative inhibitory capacity of individual allotypes.

IV. Expression of KIR3DL1

Like most other KIR, KIR3DL1 is found predominantly on the $CD56^{dim}$ subset of NK cells and a small population of (mainly $CD8^+$) T cells. The proportion of NK cells that express KIR3DL1 is approximately 10–30% and varies between individuals but is relatively stable over time within healthy individuals, while expression on T cells (approx 1–3%) is found to increase with age.[26] As NK cells differentiate and acquire KIR expression, the variegated pattern of KIR3DL1 expression is established via a bidirectional proximal promoter that acts as a probabilistic switch. Transcription in the reverse direction results in the generation of an antisense RNA, which is in turn processed into a 28-mer PIWI-like RNA[27]. This RNA species is involved in maintaining KIR silencing by directing promoter methylation. Thus, the presence of the antisense transcript is associated with a lack of KIR expression.[28] Accordingly, polymorphisms within transcription factor binding sites in the bidirectional promoter that lead to a higher probability of transcription in the forward direction are associated with a greater frequency of KIR3DL1 expression.[29] Li *et al.* identified polymorphisms within the promoter region of KIR3DL1 alleles that influence this ratio of forward and reverse activity and thus frequency of expression. They found that 3DL1*001 and KIR3DS1 are associated with a higher frequency of expression relative to 3DL1*002 and *005, which can be traced back to polymorphic positions within E2F, YY1 and Sp1 transcription factor binding sites. *3DL1*001* and *KIR3DS1* contain a SNP within the Sp1 binding site resulting in high forward promoter activity of these alleles. While *3DL1*005* also contains this SNP, it carries a second SNP in the E2F site that reduces binding and counteracts the increased forward activity associated with the Sp1 SNP. Highest levels of expression are seen with the *KIR3DS1* gene, which carries a third SNP within the YY1 binding site. This promoter-directed mechanism of variegation is consistent with the frequency of expression being predominantly controlled at the genetic level, although Yawata *et al.* have reported subtle effects on frequency and intensity of expression based on the presence of cognate HLA ligands.[23] They found that in those individuals expressing certain KIR3DL1 allotypes, heterozygous expression of Bw4 (but intriguingly not homozygous expression) results in a greater frequency, but reduced intensity, of KIR3DL1 expression. Taken together it appears that most regulation of frequency and intensity is germline encoded, perhaps overlaid with minor tuning effects from receptor/ligand interactions.

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V. Ligand Binding of KIR3DL1: the role of HLA and peptide diversity

The ligand for KIR3DL1 is present within the subset of HLA-A and HLA-B molecules that express the public epitope Bw4.[30] Originally defined serologically, this motif is determined by amino acid positions 77–83 and includes HLA-B*57, HLA-B*27 and HLA-A*24 molecules. Initial reports suggested that Bw4 epitopes on HLA-A molecules were not recognized by KIR3DL1,[30] but further study showed that HLA-A*23, A*24 and A*32 but not A*25 were indeed ligands for KIR3DL1.[31] Within the Bw4 epitope itself, there are 3 variable positions (77, 80 and 81) giving rise to at least 4 distinct amino sequences. Of particular note is the dimorphic residue at position 80 – either isoleucine (Bw4 80I) or threonine (Bw4 80T). The bifurcation of HLA-Bw4 allotypes based on position 80 produces a differential interaction with KIR3DL1, and an initial report indicated that Bw4 80I represents a stronger ligand for KIR3DL1 than Bw4 80T.[32] However, Luque *et al.* reported an NK cell specificity that preferentially recognized HLA-Bw4 80T.[33] This group examined the protection generated through the expression of a panel of HLA-B*27 allotypes. While B*2701, B*2703, B*2704, B*2705 and B*2706 (all Bw4 80T) provided protection, B*2702 (Bw4 80I) did not. Site directed mutagenesis of position 80 in B*2705 (T- > I) abolished the protection, providing direct evidence for the role of 80T. These two specificities (for 80I or 80T) were initially termed NK3 and NK4, but we now understand this to be a refection of distinct KIR3DL1 allotype specificity. The invariant R83 within Bw4 epitopes is crucial to the interaction with KIR3DL1,[34] while the effect of perturbation of L82 depends on the HLA allotype in question.[35] This suggests that residues outside of the immediate Bw4 epitope (positions 77–83) play a role in KIR interactions. In fact, in a comparison of B*1513 and B*5101 Sanjanwala *et al.* defined a role for polymorphic positions within all three class I α domains. In particular residues 67, 116 and 194 play dominant roles, which the authors suggest is due to the ability of these residues (located in the B and F pockets) to affect the conformation of the presented peptides.

In contrast to the T cell receptor, which displays very fine peptide specificity, KIR3DL1 recognizes Bw4 molecules presenting a variety of peptides. However, there is some degree of specificity in the interaction, focused on the C terminal portion of the peptide sequence. Initial studies examined the interaction of KIR3DL1 with HLA-B*2705 presented on the surface of the antigen-processing deficient cell line RMA-S. This allowed for exogenous loading of specific peptides into the class I peptide groove for interrogation by KIR3DL1.[36, 37] Peruzzi *et al.* used a panel of peptides to identify position 7 and 8 of the presented nonamer as particularly important in the KIR3DL1 interaction. Interestingly, the KIR interaction was not tied to the presence of any individual residue at these positions, suggesting that there was not a specific recognition of peptide residues. Rather, the authors speculated that certain residues at position 7 and 8 may hinder KIR3DL1 interactions either through direct interference with the KIR/HLA interaction or alternatively via the induction of conformational changes within the Bw4 epitope of the HLA molecule. To further explore the role of peptide in KIR interactions, Stewart-Jones *et al.* resolved the crystal structures of three different B*2705-peptide complexes. These included immunodominant peptides from influenza and HIV (both recognized by KIR3DL1), and EBV (not recognized by KIR3DL1).[38] The conformation and solvent exposure of the peptide residues differed between epitopes. In the non permissive B*2705-EBV peptide complex, the presence of an exposed glutamate residue at position 9 within the decamer peptide was responsible for the lack of interaction with KIR3DL1, and substitution of threonine at this position restored binding. This suggested that electrostatic repulsion of a negatively charged residue near the C-terminal end of the peptide might inhibit KIR3DL1 interaction. As one might expect from this model of interaction, KIR3DL1 polymorphism can also directly influence peptide tolerance during KIR/HLA interactions, presumably by accommodating otherwise non-permissive peptide residues. In fact, using a panel of A*2402 and B*5703 tetramers,

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Thananchai *et al.* showed that some peptide-HLA combinations bound to all KIR3DL1 allotypes tested, while others bound only to a subset or a single allotype.[39] Taken together, these studies suggest that a give-and-take relationship exists between the KIR3DL1 allotype and the presented peptide. In some cases, individual allotypes will tolerate carboxyl-terminal peptide residues, but in other cases, the level of mismatch may simply be too large.

Analysis of the pool of reported non-permissive peptides for KIR3DL1 does not show any bias for non-self or pathogen derived peptides, suggesting that this system is not tuned to avoid recognition of specific "danger associated" peptides. Instead, it appears that any given cell presents a mixture of both permissive and non-permissive peptides, which on balance is sufficient to engage KIR3DL1 and inhibit NK cell activation. In this system, any event that causes a change in the pool of peptides presented by class I – such as viral infection, transformation, or the induction of a stress response – might change the balance of peptides presented to now disfavor KIR interaction and lead to activation of that NK cell subset. A wonderfully serendipitous discovery of the potential of this system was shown by Liberatore *et al.* who found that transduction of T cells with an exogenous protein (in this case the neo selection marker) now rendered these cells susceptible to lysis by autologous NK cells.[40] This phenomenon was traced back to the presentation of a neo-derived peptide by HLA-B*27, which was not permissive for KIR3DL1 interactions and lead to the activation of the KIR3DL1^{+} NK cells and the targeting of the altered cells. In this case, as in others, serendipity translated into an understanding of actual disease-related effects. Two studies have now shown that KIR3DL1 differentially interacts with an immunodominant B*57 HIV epitope (TW10) and a naturally occurring variant thereof.[41, 42] While KIR3DL1 interacts with the wildtype peptide, the C-terminal variant escapes recognition by KIR3DL1. The power of HLA-KIR interactions to shape HIV evolution *in vivo* has recently been demonstrated by Alter *et al.*,[43] suggesting the possibility that the observed TW10 variation may be a reflection of effective immune pressure due to the KIR3DL1-B*57 interactions.

VI. The role of KIR3DL1 in disease: evidence from genetic association studies

The biological significance of the interaction of KIR3DL1 with its ligand is supported by a large number of genetic association studies that report an influence of KIR3DL1 on the acquisition, progression or therapy response to a number of pathogenic challenges (selected highlights are presented in Table 1). A role for KIR3DL1 has been found in a variety of scenarios, including viral infections, cancers, autoimmunity and transplantation. These studies also provide evidence that the functional differences seen between KIR3DL1 allotypes *in vitro* are biologically significant, as a growing number of studies find distinct effects on outcomes based on the presence or absence of specific KIR3DL1-HLA allotypes. One useful way of grouping KIR3DL1 allotypes for association analysis is based on their level of expression as detected with DX9.[44] As noted above (section III), allotypes may be detected as dim or bright DX9 staining of KIR3DL1 on NK cells. Using this criterion, allotypes such as *001 and *015 are termed "High" while others including *005 and *007 are referred to as "Low". By grouping KIR3DL1 allotypes in this manner, and stratifying HLA-Bw4 molecules based on position 80 (80I vs 80T), the Carrington lab has shown that specific subtypes can have different impacts on HIV progression, with the greatest protection being afforded by the "High" allotypes together with Bw4 80I.[44]

One of the main challenges in the interpretation of these studies (summarized in Table 1) is identifying the effector immune cell of importance. NK cells, due to their potent cytolytic ability and robust cytokine production, have the potential to affect many immune responses, particularly those to viral infections and transformation. KIR expression is also found on several T cell subtypes, and it may be KIR expression on this cell type that is critical in

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determining disease outcome. In light of recent evidence of the ability of NK cells to shape and control T cell responses, perhaps KIR expression by NK cells may critically influence the ability of NK cells to cull T cell populations and limit their activity.[45] In addition to the identity of the KIR regulated cell, the nature of the functional response (inhibition or activation) responsible for the effects seen in disease associations is not clear. Most KIR3DL1 allotypes transmit an inhibitory signal, so the effect may be due to inhibitory signaling in the KIR$^+$ cell. Paradoxically, this may lead to greater T cell response due either to protection of T cells from activation induced cell death or inhibitory signals that would prevent the elimination of T cells by NK cells activated during infection. Alternatively, it is possible that during the disease course, it is the loss of the inhibitory signal and resultant activation that influences outcomes. Thus, in contrast to a donor who lacks the KIR3DL1-HLA-Bw4 interaction, donors who carry this compound genotype possess a fully functional NK cell subset whose inhibition depends on this interaction (see discussion of education above). Loss or modification of HLA then results in strong cytolytic responses. Indeed, stratification of KIR3DL1/HLA alleles into distinct groupings with differential protection in HIV correlates with the functionality of NK cells. Accordingly, highly protective genotypes are associated with donors in whom the NK cells, in particular the KIR3DL1+ subset, have a greater functional potential and show greater cytokine and degranulation responses upon stimulation.[46] Cellular activation seems to be most likely in the case of control of viral load in HIV, where it has been shown that both the activating KIR3DS1 and the inhibitory KIR3DL1 allotypes, in the presence of HLA-Bw4, are associated with delayed progression.[44, 47]

VII. A Unique Role for KIR3DS1?

While activating and inhibitory 2D KIR are the products of distinct genes, the *KIR3DL1* locus is unique in encoding both types of receptor. *KIR3DS1* is an allele of the *KIR3DL1* locus found at high frequencies in many populations[18]. Similar to other KIR pairs, the KIR3DS1 protein product is highly conserved in the extracellular domain but differs from KIR3DL1 allotypes by virtue of its truncated cytoplasmic domain and a transmembrane lysine residue that facilitates association with the activating adaptor DAP12. Despite this remarkable degree of conservation in the ligand-binding domain, KIR3DS1 does not readily react with HLA-Bw4.[25, 48] In fact, analysis of the role of the amino acid changes in KIR3DL1 identified a cluster of four unique amino acid substitutions characteristic of KIR3DS1 (W138, S163, R166 and L199). When introduced individually into KIR3DL1 allotypes, all four 3DS1 signature residues had the potential to decrease HLA binding, although the degree of loss depended on the peptide-HLA complex in question suggesting that multiple variants may be maintained to avoid binding to a variety of Bw4 allotypes.[49, 50]

Despite the inability to directly measure KIR3DS1 interactions with HLA-Bw4 there is growing indirect evidence to support the existence of such an interaction (highlights summarized in Table 2). These data have suggested the possibility that the KIR3DS1 ligand interactions may be finely regulated – potentially at a number of levels, including the presented peptide. In such a model, KIR3DS1 activation could be limited to occasions when pathogen-, tumor-, or stress protein-derived peptides are presented in the context of HLA-Bw4. The most compelling evidence comes from HIV studies with the initial finding that *KIR3DS1*, in the presence of *HLA-Bw4 80I*, is associated with slower progression to AIDS.[47] In further support of this, NK cells from KIR3DS1$^+$ donors have been found to suppress HIV replication in HLA-Bw4 80I$^+$ target cells, and the KIR3DS1$^+$ subset of NK cells reportedly expands during acute HIV infection in HLA-Bw4 80I individuals.[51, 52] Furthermore, copy number variation analysis revealed that increasing copy number of *KIR3DS1* (in the presence of *HLA-Bw4 80I*) results in lower viral set points in HIV

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patients.[53] Interestingly, in an *in vitro* assay of viral inhibition, the KIR3DS1 copy number effect was seen only in the presence of an inhibitory KIR3DL1 allotype, suggesting the possibility of interplay between these two receptors in the balance of NK cell activation in HIV infection. These data suggest that in addition to the coordination of function between the inhibitory Yin and activating Yang in the immune system as a whole, it can also play a role at the level of an individual cell.

VIII. Structural Insight Into KIR3DL1

While the structure of the 2D KIR alone and in complex with their HLA ligand was resolved in 1999,[54] structural information on KIR3DL1 has lagged behind. This deficit in our understanding has recently been redressed with the successful generation of a high-resolution crystal structure of KIR3DL1*001 in complex with HLA-B*5701 presenting the nonamer peptide LSSPVTKSF (LF9).[55] Perhaps not surprisingly, this structural analysis showed that the mode of interaction of the D1 and D2 domains is similar to that seen with the 2D KIR, with these domains, and their connecting loops, forming an interaction face that lies perpendicularly over the Bw4 epitope and the C-terminal end of the peptide-binding groove. The D2-mediated contacts show a high degree of complementarity and are critical for the interaction with HLA-B*5701, as confirmed by targeted mutagenesis. In contrast, the D1-mediated contacts appear to be suboptimal, have poor charge complementation, and are not very sensitive to perturbation. This is in sharp contrast to 2D KIR, where variation at contact sites in the D1 domain have dramatic effects on HLA-C avidity and specificity.[56]

While the configuration of D1–D2 was in line with expectations, the location and function of KIR3DL1's characteristic D0 domain was a surprise. Although mutagenesis studies had shown that this domain acts as a "binding enhancer" during interaction with HLA molecules, the nature of this interaction was not understood.[57, 58] In fact, the crystal structure revealed that this domain clamps around the side of the peptide-HLA complex, making distinct contacts with nonpolymorphic loops, the HLA molecule, and abutting #2 microglobulin. As such, this domain likely acts as an "innate sensor" for the HLA molecule, independent of the exact HLA allotype in question. This mode of interaction may allow KIR3DL1 to accommodate a certain degree of sequence variation amongst the Bw4 epitope of its ligands. By using highly complementary interactions at both ends (D0 and D2), it allows for a degree of tolerance and suboptimal contacts in the central D1 region. As predicted both from comparison with 2D KIR and peptide substitution analysis, KIR3DL1 makes important contacts with the C-terminal end of the peptide. Residues in D1, D2, and the D1–D2 loop make direct or water-mediated contacts with serine at P8 of the presented LF9 nanomer. In agreement with previous work, substitution of this position for charged residues (in particular negatively charged residues) resulted in a loss of affinity. Of particular note, very few of the polymorphic residues found in inhibitory KIR3DL1 allotypes map to contact residues, or even the contact face. This suggests that much of the variation in function of KIR3DL1 allotypes is not due to a direct influence on binding. Instead effects from distant sites may be transmitted to the binding face to alter conformation or orientation. Alternatively, these polymorphic residues may influence other characteristics such as protein stability, higher order clustering, interaction with pathogen-derived factors, etc.

The resolution of the crystal structure also provided immediate insight into the potential of KIR3DS1 to interact with HLA. Of the four unique KIR3DS1 residues, three were involved in the interaction of KIR3DL1 with B*5701 (138, 166 and 199). Mutation of KIR3DL1 residues to mirror KIR3DS1 at these positions revealed a dominant role of 166 in the interaction with B*5701. In place of the leucine found in KIR3DL1 (with interacts with 80I of HLA-B*5701 as well as with P8 of the peptide), KIR3DS1 carries a positively charged

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arginine residue at position 166. Modeling of this residue highlighted the potential of this arginine in KIR3DS1 to clash with the invariant arginine at position 83 of the Bw4 epitope. While these data support the experimental observation that KIR3DS1 does not readily react with HLA, we have reported that a rare KIR3DS1 variant (KIR3DS1*014) that differs only at position 138 (and as such carries R166) reacts robustly with multiple HLA-Bw4 allotypes.[49] While the HLA recognition by KIR3DS1*014 was dependent on the presence of other 3DS1-like residues (in particular at position 199), it provided strong evidence that, at least under some circumstances, arginine at position 166 can be tolerated. One potential variable for the control of the common KIR3DS1*013 interaction is the presented peptide, with 166 as the sole point of direct KIR contact with the peptide. As such, it is possible that there exists a (small) subset of peptides that when presented by Bw4 alters the interaction so as to accommodate the arginine of KIR3DS1. It is interesting to speculate that this peptide may be pathogen- or stress-derived, although many attempts to identify such a peptide have as-of-yet proved unsuccessful.[59]

VIII. Conclusions

KIR3DL1/S1 receptors and their interaction with peptide loaded HLA molecules is clearly a complex system with the ability to control the activation of NK and T cell subsets. There is abundant evidence that this interaction can play an important role in many disease settings, suggesting that a thorough understanding of the system may yield valuable therapeutic interventions. Our understanding of the mechanisms behind the interaction of the polymorphic inhibitory KIR3DL1 allotypes with the highly variable HLA molecules, presenting almost limitless peptide variants has benefited from careful studies of the role of variation in each of the three components of this interaction. The resolution of the crystal structure has also provided valuable insights into the mechanisms of this binding. The challenge that now remains is to understand the role that these interactions play in health and disease through the translation of genetic disease associations into functional mechanisms, and ultimately identification of potential areas for therapeutic intervention. In contrast to our understanding of the Yin of the system, inhibitory KIR3DL1, much of the biology of the Yang, KIR3DS1 remains unclear. This is likely to remain the case until the full nature of its ligand is elucidated. Unfortunately, this question has to date proved very elusive and may require new and innovative approaches and technologies. Regardless, until the functions of KIRDS1 are resolved, the explanation for evolutionary maintenance of this unique combination locus remains an enigma and the full value of KIR3DL1/S1 Yin-Yang will remain unappreciated.

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Abbreviations

KIR	Killer Immunoglobulin-like Receptors
NK	Natural Killer
HLA	Human Leukocyte Antigen
pHLA	peptide-HLA complex
ITIM	Immunoreceptor Tyrosine-based Inhibitory Motif
Ig	Immunoglobulin

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SNP	Single Nucleotide Polymorphism
TAP	Transporter associated with antigen presentation
EBV	Epstein Barr Virus
HIV	Human Immunodeficiency Virus
SHP-1	SH2 domain-containing protein tyrosine phosphatase-1
SHP-2	SH2 domain-containing protein tyrosine phosphatase-2
IFN-γ	interferon gamma

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Table 1

Role of KIR3DL1 and KIR3DL1 Polymorphism in Disease: Evidence from Genetic Studies

Condition	Genotype	Finding	Ref
KIR3DL1			
HIV	3DL1+B*57	Decreased rate of progression to AIDS	56
	3DL1+Bw4	Frequency of the compound genotype is reduced in HIV highly exposed seronegative individuals	57
Ankylosing Spondylitis	3DL1+Bw4 80l	Increased susceptibility	58
	3DL1+Bw4 80l	Decreased susceptibility	59
Hematopoietic stem cell transplantation	3DL1+Bw4	Decreased non-relapse mortality	60
	3DL1+ (donor), Bw4-(recipient)	Lower overall survival	61
KIR3DL1 polymorphism			
HIV	3DL1 (high) + B*57	Reduced risk of acquisition of infection in HIV exposed individuals	62
	3DL1 allotypes	Reduced risk of acquisition of infection in HIV exposed individuals	62
	3DL1 high/low + Bw4 80I/80T	Decreased rate of progression to AIDS and lower viral load	42
Ankylosing Spondylitis	3DL1*F(not*004)[1]	Decreased susceptibility	63
	3DL1*004	Increased susceptibility	64

[1]3DL1*F; functional KIR3DL1 allotypes, does not include *004 as it is retained intracellulary.

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Table 2

Evidence of a functional role for KIR3DS1

Condition	Genotype	Finding	Ref
HIV	3DS1+Bw4 80l	Delayed progression towards AIDS	47
	3DS1+Bw4 80l	Protection from opportunistic infections	60
	3DS1 homozygous	Reduced risk of acquisition of infection in HIV exposed individuals	61
	3DS1+ Bw4	Increased in HIV exposed seronegative	62
	3DS1+Bw4+3DL1	Increased KIR3DS1 gene copy number associated with lower viral set point.	53
HBV	3DS1	Associated with spontaneous recovery	63
HCV	3DS1 homozygous + Bw4	Increased risk of cirrhosis	64
	3DS1+Bw4 80l	Decreased risk of hepatocellular carcinoma	65
Tuberculosis	3DS1+Bw4 80l	Decreased susceptibility	66
Cervical neoplasia	3DS1+ Bw4	Increased risk	67
Multiple Myeloma	3DS1	Decreased progression-free survival after autologous stem cell transplantation	68
Endometriosis	3DS1	Reduced susceptibility	69
Ankylosing Spondylitis	3DS1	Increased susceptibility	70,71
	3DS1	No effect	72
	3DS1+Bw4 80l	Increased susceptibility	73
HSCT	3DS1 (donor)	Decreased acute GvHD	74
Functional			
HIV	Increased inhibition of viral production by 3DS1^{+} NK cells in Bw4 80I patients. Preferential activation of KIR3DS1^{+} cells upon exposure to HIV+ Bw4 80I+ cells		51
	Expansion of KIR3DS1^{+} NK cells in acute HIV infection		52
	Increased IFN-γ production and CD107a levels in 3DS1^{+} donors at baseline and after stimulation with class I negative target cells. Not associated with Bw4 80I		75