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The Ying and Yang of *HLA* and *KIR* in Human Disease

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Abstract

Killer cell immunoglobulin-like receptors (*KIR*) are expressed on natural killer (NK) cells and subsets of T cells. The *KIR* genes are polymorphic and the *KIR* gene complex is polygenic with varying numbers of inhibitory and activating receptors. HLA class I molecules serve as ligands for the KIR. Interactions of the independently segregating *KIR* and *HLA* loci are important for recognition of targets by NK cells as well as NK cell 'licensing'. Several disease association studies indicate a role for interactions between these loci in infectious diseases, autoimmune/inflammatory disorders, cancer and reproduction. Emerging functional data supports a mechanism based on a continuum of inhibition to activation through various compound *KIR-HLA* genotypes in diseases.

Keywords

KIR; HLA; Natural killer cells; disease associations

1. Introduction

Natural killer (NK) cells are part of the innate immune arsenal and have important roles in killing virally infected cells and neoplasms, and building vasculature for nourishing the fetus in eutherian mammals. To some extent, mammals have evolved species-specific NK cell receptors that belong to structurally disparate gene families, including C-type lectin receptors in mice (Ly49) and immunoglobulin-like receptors in primates (killer cell immunoglobulin-like receptors; KIR). Their products interact with MHC class I molecules and they appear to be restively adapting to and even surpassing *MHC* evolution [1–4].

Due to their spontaneous killing of targets that either lack self MHC or express allogeneic MHC, NK cells were initially thought to be non-MHC restricted. Karrë and colleagues observed, however, that NK cells were actively inhibited by targets expressing self MHC class I [5], whereas they were able to reject bone marrow cells from β2-microglobulin deficient mice [6], the so-called "missing self hypothesis". This hypothesis suggested that NK cells recognized and killed targets lacking MHC class I, which is generally expressed on all healthy nucleated cells but can be downregulated as a result of viral infection or malignant transformation [7]. This led to a paradigm shift in the role of NK cells from being

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"null cells" to being the first line of defense. The missing self model does not entirely explain the mechanism of NK cell activation and the protection of some normal self cells with little/no expression of MHC against NK cell attack [8]. Therefore, the presence of activating receptors on NK cells and cognate ligands on infected or transformed cells was hypothesized in the 'induced self recognition' hypothesis [9]. Indeed, multiple activating receptors that recognize self protein (reviewed in [10]) have been implicated in NK cell killing of virally infected or transformed cells, supporting the hypothesized recognition of 'induced self' by NK cell receptors. Along these lines, the mouse activating NK cell receptor Ly49H was shown to recognize the virally encoded MHC-like protein produced by mouse cytomegalovirus, m157 [11].

Once NK cell receptors that recognize MHC class I molecules appeared in mammals, they evolved dramatically. Most of these receptors belong to two main families, the killer cell lectin-like receptor family (KLR) and the killer cell immunoglobulin-like receptor (KIR) family, which have been preferentially expanded across different species. The KLR, for example, have expanded in rodents (Ly49), while the KIRs have expanded in primates, a quintessential example of convergent evolution. Although these distinct sets of receptors do not share a common evolutionary ancestor, they nevertheless have remarkable similarities in that they are polygenic, highly diverse, variegated in expression on NK cell clones, and functionally equivalent. *Ly49* and *KIR* haplotypes vary in both the number and types of genes present, some of which are inhibitory and some activating. The presence of remnants of *KIR* in rodents [12] and *Ly49* in primates [13] [14] suggests that the two receptor gene families evolved independently since the existence of their last common ancestor, perhaps in response to species specific pathogens.

For simplicity in this review, we attribute the consequence of *KIR* variation on human disease to one cell type, NK cells. In some cases, functional data have employed purified NK cells showing that this cell type is at least mostly responsible for the observed genetic association. However, KIR are also expressed on subsets of T cells, so some of the disease associations mentioned below could actually be due to the effects of KIR in modulating T cell activity, and indeed we note the involvement of T cells when it is known (see sections 5–8 below).

2. *KIR*

The *KIR* gene cluster on chromosome 19q13.4 within the leukocyte receptor complex consists of a centromeric and telomeric region separated by *KIR2DL4*, which is present on virtually all haplotyes (Fig. 1). To date, 14 *KIR* genes and 2 psuedogenes have been described. The *KIR* gene cluster is flanked by *KIR3DL3* at the centromeric end and *KIR3DL2* at the telomeric end, both of which are present on virtually all haplotypes [15]. Recently, a novel and divergent *KIR* gene, termed *KIR3DX1*, of unknown function was identified approximately 180 kb centromeric to the *KIR* cluster and between the two *LILR* clusters (Fig. 1). This gene is conserved throughout primates, suggesting that it is the ancestral gene from which all other *KIR* were derived [16]. Interestingly, while it is maintained as a single copy in primates, it has been expanded in cattle [17]. Variability in gene content at the *KIR* locus appears largely due to gene duplication [18] and non-allelic homologous recombination [19]. Two basic haplotypes have been defined on the basis of gene content, and are termed haplotypes A and B. Haplotype A is uniform in terms of gene content and is composed of five inhibitory genes (*KIR2DL1, 2DL3, 3DL1, 3DL2, 3DL3*), one activating gene (*KIR2DS4*), and *KIR2DL4*, which may have both inhibitory and activating capacity. *KIR2DL4* has a charged amino acid in the transmembrane domain that interacts with the activating motif (ITAM) of FCεRI-γ [20], as well as a long cytoplasmic tail containing a single inhibitory motif (ITIM). Interestingly, many A haplotypes possess

null variants of both *KIR2DS4* [21] and *KIR2DL4* [22] that are not expressed on the cell surface. Thus, these haplotypes technically possess no functional activating *KIR*. The B haplotypes contain variable numbers of activating and inhibitory receptors and are the primary contributors to the extraordinary differences in gene profiles observed in distinct ethnic populations across the world [3].

3. *KIR* ligands

The inhibitory KIR2DL1, 2DL2, and 2DL3 recognize HLA-C ligands. Each HLA-C allotype belongs to one of two ligand groups based on a dimorphism at position 80 in the alpha helix: group 1 (HLA-C1), which has asparagine, and group 2 (HLA-C2), which has lysine at position 80 (Fig. 2). Position 44 in the D1 domain of KIRs appears to determine their ability to discriminate between the two groups of HLA-C allotypes [23], where KIR2DL1 binds HLA-C2 allotypes and KIR2DL2/2DL3 bind HLA-C1. Recent data, however, suggest that KIR2DL2/2DL3 can also bind weakly to some HLA-C2 allotypes *in vitro* [24]. The authors postulate an interesting evolutionary model whereby the interactions between HLA-C1 and KIR2DL2/2DL3 existed prior to the appearance of the HLA-C2 epitope. The eventual appearance of the HLA-C2 epitope then selected for novel KIR variants that interacted with HLA-C2. The current binding specificities are indicative of a continually evolving system where the newer KIR2DL1 receptors exclusively bind HLA-C2 and the older KIR2DL2 and KIR2DL3 have retained their functional, although weaker, interactions with HLA-C2. KIR3DL1 is known to bind HLA-B allotypes with the Bw4 motif [25] [26], although some low affinity binding with Bw6 has also been reported [27]. The dimorphic position 80 among the Bw4 allotypes affects its interaction with KIR3DL1 subtypes, where HLA-B Bw4- containing allotypes with isoluecine at position 80 (Bw4-80I) generally exhibit stronger inhibition through KIR3DL1 [25, 27, 28]. However, Bw4 allotypes with threonine at position 80 (Bw4-80T), such as HLA-B*2705, appear to be better ligands for certain 3DL1 subtypes [29].

Other receptor-ligand relationships among KIR and HLA include KIR2DL4 specificity for HLA-G, which is primarily expressed on fetal trophoblasts, thymic endothelial cells and cornea [30], and KIR3DL2 specificity for HLA-A3 and A11 [31]. The activating receptors KIR2DS1, 2DS2 and 3DS1 share sequence similarity in their extracellular domains with their corresponding inhibitory counterparts (KIR2DL1, 2DL2/2DL3 and 3DL1, respectively) and are thought to share HLA ligand binding specificities as well. KIR2DS1 has been shown to bind weakly to HLA-C2 allotypes [32], which appears to have functional significance [33–35], and KIR2DS2 may bind weakly to HLA-C1, though this has not been conclusively established [33]. Until recently, expression of KIR3DS1 was in doubt, but there is now convincing evidence that it is indeed expressed [36–39]. KIR3DS1 shares >95% similarity with KIR3DL1 in its extracellular domain, but there is no direct evidence of interactions between 3DS1 and Bw4 allotypes. Still, genetic epidemiological [40, 41], functional [42], and population genetic data [3] strongly support such an interaction. KIR2DS4 is thought to interact with HLA-Cw4 alleles [43] and possibly with a non-HLA ligand expressed on melanoma cells [44]. Ligands for KIR2DL5, 2DS5, 2DS3 have not yet been identified.

4. *KIR/HLA* interactions

HLA class I genes map to chromosome 6, unlinked to the *KIR* genes on chromosome 19. Thus, the inheritance and expression of the genes encoding the receptors and their ligands are physically independent of one another other. It is therefore possible that a certain *KIR*, its ligand, or both might be absent in a given individual, each of which results in a functionally null situation. KIR also exhibit variegated expression on NK cells (i.e. a given

KIR gene is expressed on some, but not all NK cell clones within an individual), adding another dimension to the variability and complexity of the system. Once acquired, the pattern of expression of inherited *KIR* genes remains stable in NK cell clones under varying cell culture conditions and activation stimuli [45]. Expression of *KIR* is controlled at the transcriptional level by epigenetic changes, primarily by methylation of CpG islands surrounding the transcriptional start site [46]. Identification of bidirectional promoters for *KIR* establishes yet another parallel between mouse and human NK cell receptor genes. In humans, bidirectional promoters control expression of *KIR* by switching the direction of transcription during the development of NK cells. Reverse transcripts are found in immature NK cells not expressing KIR, but these transcripts are absent in mature KIR-expressing NK cells, suggesting that reverse transcription blocks gene activation in immature and precursor NK cells [47]. Thus, if the promoter for a given *KIR* gene is switched in a forward position during development of the NK cell clone, then that mature clone will express the gene, but if the promoter is switched in the reverse direction, the clone will not express that *KIR* gene. The switch is stochastic, resulting in variegated expression of *KIR* and a repertoire of subpopulations of NK cells expressing different combinations of cell surface activating and inhibitory receptors that together are capable of responding to a wide variety of stimuli.

It has become increasingly clear that the strength of HLA-KIR interactions has functional significance and can influence disease susceptibility. This is exemplified by the interactions between HLA-C and inhibitory KIR2D where KIR2DL1/HLA-C2 (and probably KIR2DL2/HLA-C1) appears to confer stronger inhibitory responses than does KIR2DL3/HLA-C1 [48, 49] (Fig. 3). Allelic variation also plays a role in determining the strength of the interaction. Some allotypes of KIR3DL1, for example, are expressed at high levels, while others are expressed at low levels, which in turn correlates with level of binding to HLA-B Bw4 ligands [50, 51]. Allelic variants can also differ in terms of the frequency of NK cells that express them [51]. Disease association data are now accumulating and indicate that these differences are very significant in determining the outcome to infection [2, 52].

Interactions between KIR and their cognate HLA ligands can also be affected by peptides present in the binding groove of the HLA molecule [53–55], particularly the residues at positions 7 and 8 [56]. KIR3DL2 was shown to bind to HLA-A3 and A-11 only when specific EBV peptides were used to fold HLA tetramers [57]. Binding of KIR3DL1 to some HLA-A and HLA-B allotypes containing the Bw4 motif has also been shown to be dependent on bound peptide [58].

While the contribution of HLA class I ligands in *KIR* gene expression is not perfectly clear, there is evidence that expressed HLA ligand does indeed modulate the frequency of NK cells expressing cognate inhibitory receptor and its level of expression [51]. Expressed HLA ligands are also known to be crucial to NK cell tolerance and education. The so-called “at least one model” assumed that each NK cell had at least one inhibitory receptor specific for self MHC class I that would account for self-tolerance [45, 59]. However, in view of the stochastic expression of KIR, this model seems unlikely. Indeed, NK cells from MHC class I deficient mice do not kill their MHC class I deficient targets [8]. Two models have recently been proposed to explain this self-tolerance. The first model purports that NK cells expressing at least one inhibitory receptor recognizing self MHC class I are allowed to mature and become functionally competent or “licensed”, while NK cells that do not possess at least one functional inhibitory interaction are hypo-responsive and therefore “unlicensed” [60]. The other model, referred to as the “disarming” model, proposes that NK cells that do not express inhibitory receptors for self-MHC are chronically stimulated and consequently become anergic [61]. Therefore, inhibition during NK cell maturation is a critical requirement for NK cells to acquire cytotoxic potential. Whether or not human NK cell activity is regulated in a similar manner is not entirely clear, but recent data suggest that this

might be the case. Anfossi *et al* provided the first evidence of licensing in human NK cells by showing that peripheral NK cells lacking inhibitory KIR for self MHC class I molecules are present in human peripheral blood and are hyporesponsive to various stimuli [62]. The authors propose a role for KIR-MHC class I inhibitory interactions in the calibration of NK cell potency [62]. Kim *et al* have also shown that specific *KIR* and *HLA* alleles are associated with the level of NK cell responsiveness, suggesting a role for "licensing" of NK cells in humans [63].

A variety of *HLA-KIR* compound genotypes have been implicated in disease pathogenesis and resistance to viral infections, autoimmune diseases, inflammatory disorders and cancers (listed in Table 1). Generally, genotypes that theoretically lead to lower inhibition and higher activation appear to be beneficial in viral infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV), whereas activating genotypes constitute a risk for susceptibility to autoimmunity and perhaps cancers that have an inflammatory component to the disease pathogenesis (Fig. 4).

5. VIRAL INFECTIONS

5.1. Human Immunodeficiency Virus (HIV)

KIR3DL1 and *KIR3DS1* segregate as alleles of the same locus and share about 97% sequence similarity in their extracellular domain, suggesting that they may bind similar ligands. HLA -Bw4 molecules are ligands for KIR3DL1, particularly Bw4-80I [25, 27, 28]. We observed that in individuals infected with HIV, the combination of *KIR3DS1* with its putative ligand *HLA-B Bw4-80I* was associated with slower progression to AIDS, lower mean viral load, and protection against opportunistic infections [40, 41]. Subsequently, Alter *et al* demonstrated that NK cells expressing KIR3DS1 strongly and significantly inhibited HIV-1 replication in cells expressing HLA-B Bw4-80I as compared to NK cells that do not express KIR3DS1, providing the first functional support for the influence of KIR3DL1/S1 and Bw4-80I on anti-HIV NK activity [42]. KIR3DS1 positive NK cell clones were preferentially activated by HIV-1 infected target cells expressing HLA-B Bw4-80I, resulting in lysis of these cells. These data indicate that NK cells identify HIV infected cells actively through KIR3DS1 and Bw4-80I interactions. The necessity to have KIR3DS1 on the NK cells and Bw4-80I on the infected target supports a model in which KIR3DS1 binds directly or indirectly to Bw4-80I, perhaps in complex with specific HIV peptides or stress-induced self peptides produced in response to HIV infection. In a more recent study involving 60 treatment-naïve individuals with early infection, Long and colleagues observed that presence of *KIR3DS1* was associated with higher NK cell effector function as measured by IFN-γ production and CD107a expression *in vitro* [64]. This effect was partially, but not completely dependent on the presence of B*57 and B*58, both of which are Bw4-80I allotypes. The presence of *KIR3DS1* was also associated with lower viral load levels and diminished CD8+ T cell activation, which is an important marker of disease progression.

A study of twenty five HIV exposed uninfected intravenous drug users from Vietnam found transcription of *KIR3DS1* to be significantly higher than *KIR3DL1* in *KIR3DS1/3DL1* heterozygous individuals and there was expansion of NK cells expressing KIR2DL3 in HLA-C1/C1 individuals who were $KIR2DS2^{-}/2DL2^{-}$ [65]. *KIR3DS1* homozygosity was also found to be significantly increased in HIV exposed seronegative intravenous drug users and HIV negative partners of sero-discordant couples [66]. These results are somewhat in keeping with previous data showing that HIV exposed seronegative sex workers carried more inhibitory receptors in the absence of their cognate HLA ligands as compared to the seropositive sex workers [67]. These individuals also had an increase in *KIR* AB haplotypes which are characterized by increased numbers of activating *KIR*.

KIR3DL1 has remarkable allelic diversity and the alleles have been shown to vary in their expression patterns on NK cells to the extent that they can be grouped into high (referred to as *KIR3DL1*h*), low (referred to as *KIR3DL1*l*), or no expression groupings [50, 51] [68] (the latter of which involves a single allele, *KIR3DL1*004*). KIR3DL1*h allotypes show higher affinity for their Bw4 ligands, particularly with Bw4-80I, which probably leads to greater inhibition [51]. We recently analyzed our AIDS cohorts for effects of *KIR3DL1* alleles in the presence of their Bw4 ligands and showed that individuals possessing the high inhibitory allotypes, *KIR3DL1*h*, along with their *Bw4-80I* ligands had the lowest mean viral loads and progressed at a slower rate to AIDS relative to other *KIR3DL1/HLA-B* genotypes (individuals with *KIR3DS1/Bw4-80I* were completely excluded from the study) [69]. While these results seem to contradict the model in which NK cell activation is protective (based on the protective effect of *KIR3DS1/Bw4-80I* in the same cohort), a model incorporating the importance of inhibition in NK cell education unifies consistently results from this study with previous studies that indicate a protective role for NK cell activation against HIV. Since interactions between inhibitory KIR and MHC class I are important in establishing tolerance to healthy cells as well as the activation potential of mature NK cells [60, 62, 63, 70], it follows that the stronger, more inhibitory interactions conferred by KIR3DL1 during NK cell development lead to a fiercer NK cell response when ligand is downregulated/lost during viral infection. Surprisingly, *KIR3DL1*004*, which is not expressed on the cell surface was the single most protective *KIR3DL1* allele against HIV disease progression and viral load and this protection was completely dependent on the presence of *Bw4*. While there are no apparent explanations for this observation, it is possible that *KIR3DL1*004* has an as yet undefined intracellular function or, alternatively, it may be in linkage disequilibrium with another locus that confers protection against the virus.

Overall, studies reported to date indicate that *HLA-KIR* combinations with strong activation potential are protective against HIV and point decidedly to the *KIR3DL1/S1* locus as most important in this regard.

5.2. Hepatitis C Virus (HCV)

Along the lines observed for HIV, compound genotypes of *KIR* and *HLA* class I that are expected to be relatively activating have also been implicated in outcome to HCV infection. As mentioned above, previous data have suggested that KIR2DL1/HLA-C2 may confer stronger inhibitory responses than does KIR2DL3/HLA-C1 [48, 49]. In individuals infected with a low-dose viral inoculum, the genotypic combination of *KIR2DL3/HLA-C1*, which theoretically results in weaker inhibitory signals (and therefore a lower activation potential), was protective in terms of spontaneous clearance of the virus [71]. Another study has also implicated a role for *KIR2DL3* in clearance of HCV [72].

Using an *in vitro* model of infection with influenza A virus, Ahlenstiel *et al* recently provided functional data that strongly supports a lower threshold for activation conferred by KIR2DL3/HLA-C1 interactions as compared to KIR2DL1/HLA-C2 interactions [49]. In order to compare the inhibitory effect of KIR2DL3/HLA-C1 with that of KIR2DL1/HLA-C2, individuals were selected who were homozygous for haplotype A and homozygous for either HLA-C1 (KIR2DL3 ligand) or HLA-C2 (KIR2DL1 ligand) (Figs. 1 and 3). NK cells from *KIR2DL3/HLA-C1* individuals secreted more IFN-γ at earlier time points after infection and displayed greater degranulation than did NK cells from *KIR2DL1/HLA-C2* individuals. These results provide direct evidence for the differential level of inhibition associated with the presence of the *KIR2DL3/HLA-C1* genotype as compared to *KIR2DL1/HLA-C2* and underscore the functional significance of such a difference in response to viral infection.

5.3. Herpes Viruses

NK cells are important in herpes virus infections since individuals deficient in NK cells are particularly susceptible to these infections [73]. In order to evade the immune system, cytomegaloviruses (CMV) encode several proteins that interfere with MHC class I expression [74], potentially rendering infected cells more susceptible to attack by NK cells. In a case study of a child with a novel immunodeficiency syndrome and recurrent CMV infection [75], the entire population of NK cells from this patient expressed KIR2DL1 and the child also possessed the KIR2DL1 ligand, HLA-C2, raising the possibility that the strongly inhibitory KIR2DL1/HLA-C2 combination crippled NK cell activity and prevented the cells from mounting a protective response against CMV. Further evidence for KIR-mediated protection in CMV infection stems from a report demonstrating that activating *KIR* are protective against CMV reactivation during T cell replete stem cell transplantation [76]. Thus, as in other viral infections, NK cell activation appears to be protective in CMV infection. On the other hand, NK cell activation might be detrimental in a situation where immune activation is undesirable. Indeed, Price *et al* found that activating *KIR* predisposed to immune restoration diseases (defined by reactivation of quiescent opportunistic infection after combination antiretroviral therapy) associated with herpes virus infections [77].

5.4. Other infections

Mycobacterium tuberculosis is highly endemic in some parts of the world. In a recent study, Mendes *et al* found a significantly higher frequency of *KIR2DL1* and *KIR2DL3* in patients, although after correction for multiple comparisons, only *KIR2DL3* remained weakly significant [78].

The role for NK cell responses to protozoa remains poorly understood. In the case of malaria, *P. falciparum* erythrocyte membrane protein I (*Pf*EMP) downregulates IFNγ production by NK cells, NKR+ γδ T cells and αβ T cells [79], as well as NK cell cytotoxicity [80]. So far, studies involving NK cell receptors and responses in malaria have been very contradictory and require validation (reviewed by Hansen, D *et al*) [81]. However, carriers of *KIR3DL2*002* produced higher levels of IFNγ in response to activation by *P. falciparum* infected red blood cells (RBCs), which is intriguing since RBCs do not express HLA ligands [82]. NK cells are a major source of IFNγ in early malarial parasite infection and NK cell activation may be regulated by crosstalk with the myeloid component of the immune system [83].

6. Autoimmunity and Inflammatory disorders

KIR associations with susceptibility to autoimmune/inflammatory conditions invariably point to the short chain activating *KIR*. Activating *KIR* are evolutionarily younger, probably having arisen from inhibitory homologues [84]. Variation in frequencies of activating *KIR* across diverse ethnic populations is extensive [3], but allelic diversity is quite limited as compared to inhibitory receptors [85]. The phenotypic frequencies of activating *KIR* and their ligands (or putative ligands) show strong negative correlations across populations, in contrast to weak positive correlations between various inhibitory *KIR* genes and their ligands [3]. These data suggest that there are selection pressures to maintain a consistently low frequency of corresponding activating KIR receptors and their ligands, perhaps in part due to selection pressures from autoimmune diseases.

Several conditions involving vascular damage and inflammation have shown association with the activating *KIR2DS2*. $CD4^{+}CD28^{null}$ T cells, which are expanded in rheumatoid arthritis (RA) and cause endothelial damage, were found to express KIR2DS2 in the absence of inhibitory KIR2DL2 in this condition [86]. Further, the frequency of *KIR2DS2* was increased in RA patients with vasculitis in comparison to normal controls and RA patients

without vasculitis [87]. HLA-Cw*03, an HLA-C1 allotype and therefore a putative ligand for KIR2DS2, was also increased in subjects with vasculitis, although this was not true for other C1 alleles [87]. Thus, it is possible that KIR2DS2 recognizes a specific HLA-Cw03-peptide complex generated during RA vasculitis. Similarly, $CD4^{+}CD28^{null}$ T cells are also present in the inflammatory infiltrate of atherosclerotic plaques in acute coronary syndrome and they express KIR2DS2 [88]. Other *KIR/HLA* associations with distinct clinical manifestations of RA [89] include the *KIR2DL3*$^{+}$*/2DS3*$^{-}$ genotype, present in patients that were diagnosed early, and *KIR2DS1* and *KIR3DS1*, which are higher in patients with bone erosions. *KIR2DL2/2DS2* were significantly increased in patients with extra-articular manifestations, including vasculitis as previously reported [89]. *KIR2DS2* in the absence of *KIR2DL2* (genes that are in strong positive LD) was also observed to be increased among scleroderma patients [90].

Activating B haplotypes of *KIR* [91] and *KIR2DS1* alone [92] or in combination with *HLA-Cw6* (a C2 ligand for KIR2DS1) have been reported to associate with psoriasis [93]. We were also able to delineate the effect of *HLA* and *KIR* compound genotypes in psoriatic arthritis [94]. Based on the data, a model was proposed in which a gradient of more activating to more inhibitory compound genotypes of *KIR2D* and *HLA-C* appear to influence susceptibility to psoriatic arthritis [94]. Genotypes conferring highest activation (*KIR2DS1* and/or *KIR2DS2* with either *HLA-C1* or *C2* homozygosity) associated with greatest susceptibility whereas the genotypes conferring maximum inhibition (absence of activating receptors *KIR2DS1* and *KIR2DS2* and presence of both the inhibitory ligands *HLA-C1* and *C2*) were protective.

Activating *KIR* gene profiles have also been associated with other inflammatory conditions such as endometriosis [95], birdshot chorioretinopathy [96], idiopathic bronchiectasis [97] primary sclerosing cholangitis [98], and type I diabetes mellitus [99] [100]. No doubt the list will continue to grow, with the most reliable conclusions being based on precise clinical data and large sample sizes. As in all genetic epidemiological studies, functional evidence for interaction between the short chain KIRs and putative ligand is necessary to support the various genetic models of predisposition to autoimmune conditions.

7. Cancer

Loss of MHC class I molecules on tumors evokes a role for NK cells in elimination of the transformed cell. Higher levels of KIR-mediated inhibition may also facilitate tumor escape, as has been shown for melanoma where the compound genotype *KIR2DL2/2DL3/HLA-C1* was more frequent in patients as compared to controls [101] and *KIR3DL1/Bw4 80I* was marginally higher in patients with metastatic melanoma [102]. A role for KIR2DS4 was proposed in melanoma through its binding to non-HLA ligands expressed on melanoma cell lines and primary melanoma [44], but this data contrasts with a study showing no difference in the frequency of *KIR2DS4* in patients vs. controls [101]. Inhibitory *KIR* (*KIR2DL1*, *2DL2* and *2DL3*) were also present at significantly higher frequencies among patients with leukemia [103], and it has been suggested that they may contribute to a lack of NK or CTL antitumor responses in renal cell carcinoma [104]. *KIR2DL5A* and *2DL5B* genes were more frequent in patients with NK type lymphoproliferative disease of granular lymphocytes [105]. Along the same lines, the activating receptors *KIR3DS1* and *KIR2DS1* associate with protection in a familial study of Hodgkin's lymphoma [106].

Activating *KIR* genotypes may have opposite effects on distinct malignancies depending on whether inflammation is or is not a major component of tumor pathogenesis. Unlike the susceptibility effects of inhibitory *KIR-HLA* genotypes on cancers in which an inflammatory component plays no apparent role in the pathogenesis, we have observed that

strongly inhibitory *KIR-HLA* genotypes were actually protective against cervical neoplasia [107]. NK cell activation may contribute to a chronic inflammatory state in response to human papilloma virus, the causative agent of cervical cancer, setting the stage for carcinogenesis. An increased number of activating *KIR* was also found to be associated with nasopharyngeal carcinoma (NPC), a cancer that is strongly associated with EBV infection [108]. It will be important to determine whether consistent results are observed with other cancers that clearly involve inflammation in the pathogenesis, such as gastric cancer and colon cancer. On the other hand, *KIR3DS1* with *Bw4-80I* allotypes protected against the development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus infection [109], in spite of a probably role for inflammation in the development of HCC in some cases.

Abnormal expression of KIR has been associated with various malignant conditions. Expression of KIR3DL2 (but not other KIR) on phenotypically abnormal T cells was observed in patients with Sézary syndrome. [110]. Inhibitory KIR are also expressed on subsets of T cell large granular lymphocytic leukemia (T-LGL) [111] and increased disease severity was associated with absence of HLA ligands for the expressed KIR [112]. KIR are also expressed on NK-LGLs [111] and activating KIR were prominent among those that were expressed [113].

8. Reproduction

Pre-elampsia is a condition caused by inadequate extravillous trophoblast invasion into the maternal spiral arteries, which results in poor placental perfusion [114]. Uterine NK (uNK) cells, which account for 50–90% of the leukocytes in the decidua, are $CD56^{bright}$ and produce cytokines, chemokines and angiogenic factors thought to be involved in the remodeling of the spiral arterioles during pregnancy [115]. They also express KIR2D that recognize HLA-C allotypes. The fetal trophoblast expresses HLA-G, HLA-E and HLA-C [116], only the latter of which is polymorphic. A predominance of homozygosity for haplotype *A* in pre-eclamptic mothers combined with the presence of *HLA-C2* in the fetus [117] suggested that strong inhibition of decidual NK cells via KIR2DL1 and HLA-C2 leads to strong uNK cell inhibition, which in turn impairs the remodeling of maternal blood vessels. Correspondingly, activating *KIR* appeared to decrease the likelihood of pre-eclampsia in a cumulative manner. Given the extreme consequences of inappropriate maternal-fetal interactions, more selection pressure may be imposed on *KIR* loci through its effect on reproductive diseases than through that of any other type of disease, including infectious diseases.

A balance in the level of activation/inhibition may be necessary in reproductive success in that excessive activation, like excessive inhibition, of NK cells could be detrimental in the maintenance of pregnancy. NK-like large granular lymphocytes have been implicated in alloimmune reactions against the fetus and their numbers are increased in the uterus and periphery in mothers who tend to abort [118]. Decreased frequency of inhibitory *KIR* or increased numbers of activating *KIR-HLA* ligand combinations are suggested to associate with miscarriages [119] [120] and recurrent abortions [121]. These studies are small and need confirmation in larger cohorts.

KIR2DL4 has been of particular interest for its role in maternal-fetal interactions because it binds HLA-G, which is expressed on trophoblasts. Yan *et al* showed that cell surface expression of KIR2DL4 was significantly higher in normal controls as compared to those with recurrent spontaneous abortion [122]. In spite of these studies, the absolute necessity of KIR2DL4 in/on uNK cells has been ruled out, since women who are missing the *KIR2DL4* gene altogether have had successful pregnancies with apparently healthy children [123, 124]

9. Summary

Models regarding the role of *KIR* in diseases have been as dynamic and fickle as the locus itself. Many of the models that have been generated based on genetic data are inconsistent with one another and require functional data to clarify the biological role of KIR in the pathogenesis of these diseases. Nevertheless, some consistent threads have been forthcoming, including the association of activating KIR genotypes with increased risk of autoimmune disease and decreased risk of some infectious disease outcomes. Further efforts in determining KIR ligand specificities and affinities will greatly enhance our ability to define the role of KIR in human disease, and in turn, to potentially apply this knowledge clinically. Even at this early point in our efforts to characterize KIR, the astonishing population genetic, evolutionary, and biological properties of this locus that have been uncovered so far have provided a daily dose of mental vitamins to those of us fortunate enough to have landed in this field.

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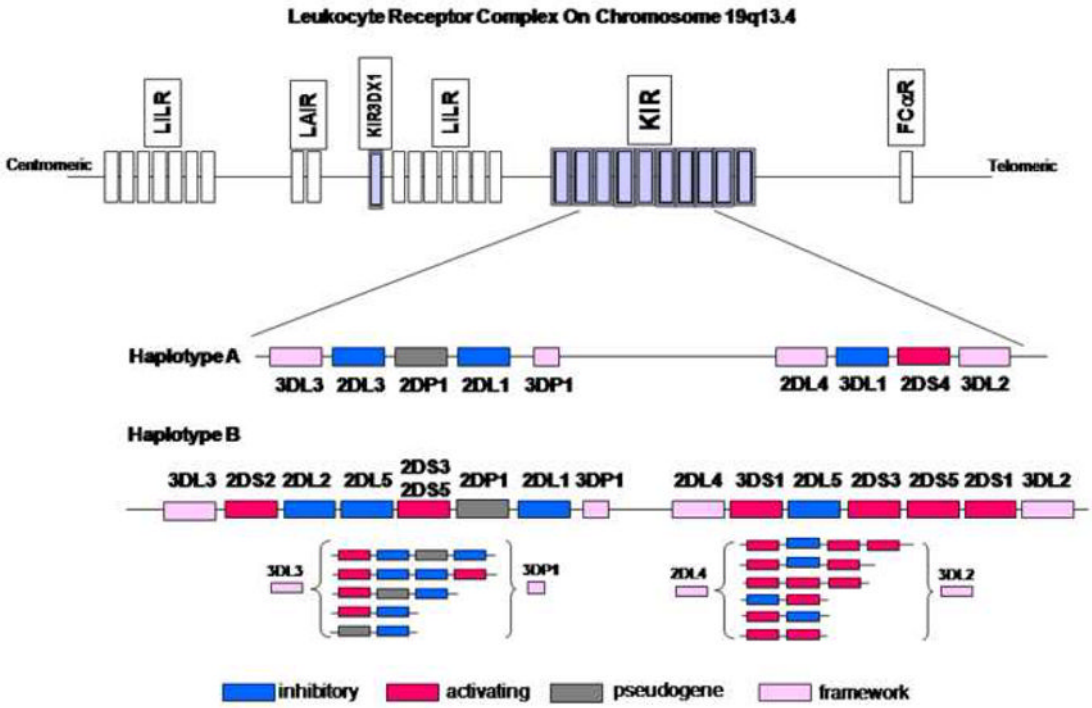

Figure 1. Genomic organization of the *KIR* gene cluster

The *KIR* gene cluster is located on chromosome 19q13.4 within the Leukocyte Receptor Complex. *KIR* haplotypes vary extensively in gene content. The *A* haplotype is fixed in terms of gene content, but the *B* haplotypes are characterized by variable gene numbers (shown in brackets). Framework genes (pink boxes) are present on all haplotypes. The ancestral *KIR* gene *3DX1* is also shown.

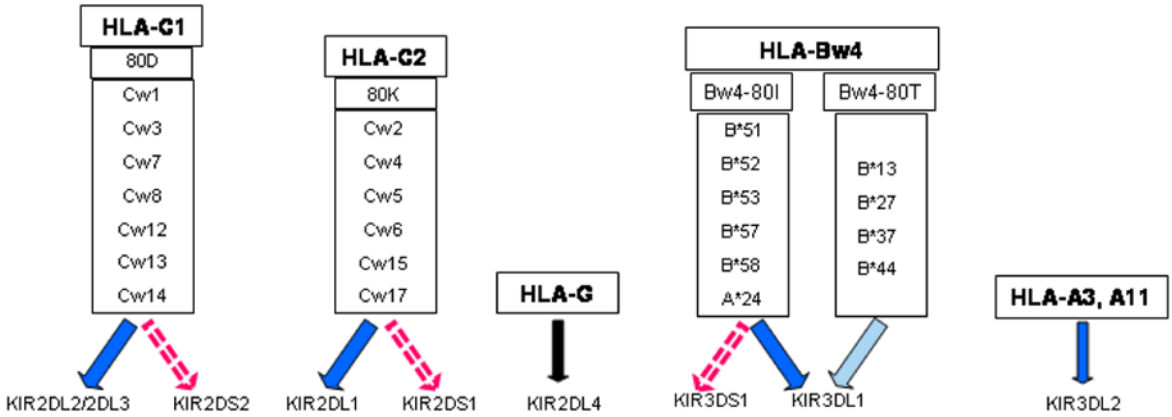

Figure 2. HLA-ligand binding specificities for KIR

Alleles belonging to the KIR ligand groups HLA-C1/C2 and Bw4 80I/80T are listed in the boxes. The activating receptors KIR2DS2, 2DS1 and 3DS1 are thought to exhibit ligand specificity similar to the corresponding inhibitory counterparts, although their interactions are much weaker (depicted as smaller red broken arrows). The interaction of KIR3DL1 with Bw4 80I (dark blue arrow) is thought to be stronger than that with Bw4 80T (light blue arrow). Ligands for KIR2DL5, 2DS3, 2DS4, 2DS5 and 3DL3 have not been identified.

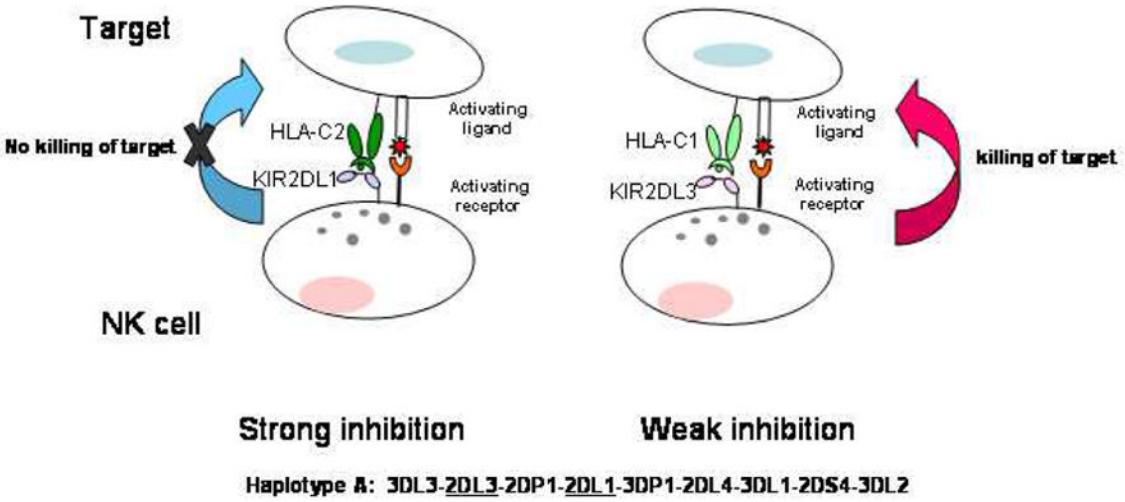

Figure 3. Functional model for KIR-HLA mediated hierarchy of inhibition

The cartoon shows possible KIR-HLA interactions in an individual homozygous for the A haplotype and homozygous for either *HLA-C2* (left side) or *HLA-C1* (right side), based on the findings of Ahlenstiel *et al* [49]. Interaction of KIR2DL1 with HLA-C2 results in strong inhibition that is difficult to overcome by simultaneous activating signals, and thus there is no killing of the target in this model. The weaker KIR2DL3-HLA-C1 interaction, on the other hand, can be overridden by signals through activating receptors upon appropriate ligand binding, resulting in lysis of the target.

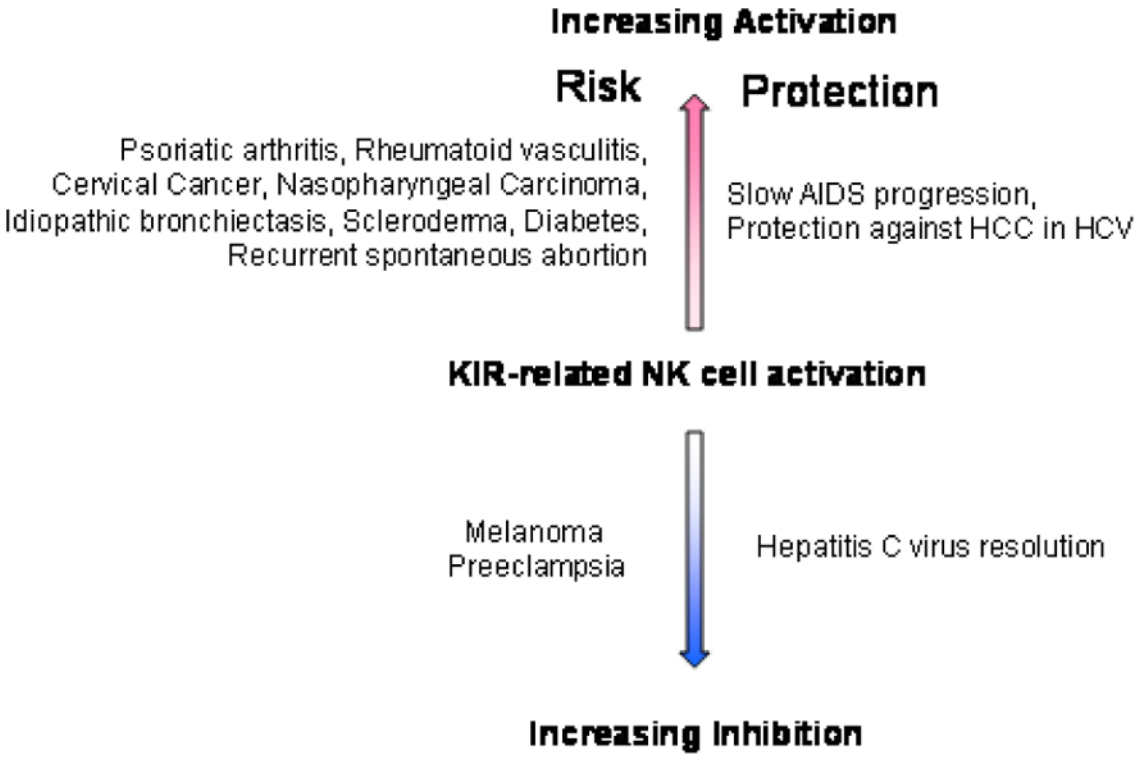

Figure 4. Summary of KIR mediated NK cell activation/inhibition in diseases

Distinct KIR and HLA ligand pairs generate a hierarchy of NK cell activation. Both increased activation and inhibition are associated with susceptibility to and protection against a variety of diseases.

Table 1

*KIR-HLA*disease associations

Disease	KIR-HLA ligand pair	Effect	Ref.
INFECTIOUS DISEASES			
HIV	*KIR3DS1/Bw4-80I*	Slower progression	[40]
	*KIR3DL1*004/Bw4*	Slower progression	[69]
	*KIR3DL1*h/ Bw4 80I*		
	KIR3DS1	Reduced risk of infection	[64, 65, 67]
HCV	*KIR2DL3/HLA-C1* homozygosity	Resolution of infection	[71]
Human cytomegalovirus (HCMV)	KIR2DL1 expression on all NK cells	Recurrent CMV infection	[75]
	>1 activating *KIR* in donor in bone marrow transplantation	Protection from CMV reactivation in the recipient.	[76]
Herpes simplex virus (HSV)	*KIR3DS1* in absence of *Bw4*	Reactivation of HSV during IRD in HIV	[77]
M. tuberculosis	*KIR2DL1; KIR2DL3*	Susceptibility	[78]
P. falciparum	*KIR3DL2*002*	High response to infected RBCs	[82]
AUTOIMMUNE AND INFLAMMATORY CONDITIONS			
Psoriatic Arthritis	*KIR2DS1/2DS2; HLA-Cw* group homozygosity	Susceptibility	[94,
Psoriasis	*KIR2DS1/HLA-Cw06*	Susceptibility	[92]
	KIR2DS1; KIR2DL5; KIR haplotype B	Susceptibility	[91]
Rhuematoid Vasculitis	*KIR2DS2/HLA-Cw03*	Susceptibility	[87]
Scleroderma	*KIR2DS2+/2DL2−*	Susceptibility	[90]
Acute Coronary Syndrome	De novo expression of KIR2DS2 on $CD4+CD28^{null}$cells	Susceptibility	[88]
IDDM	*KIR2DS2/HLA-C1*	Susceptibility	[99]
Endometriosis	*KIR3DS1/ Bw4*	Protection	[95]
Birdshort Chorioretinopathy	Weak inhibitory *KIR/HLA* combinations and activating *KIR* in HLA-A*29+ individuals	Susceptibility	[96]
Idiopathic Bronchiectasis	*HLA-C1/C1 and 2DS1/2DS2*	Susceptibility	[97]
Primary Sclerosing Cholangitis	*KIR3DL1/Bw4; KIR2DL1/HLA-C2*	Protection	[98]
CANCER			
Malignant Melanoma	*KIR/2DL2/2DL3; HLA-C1*	Susceptibility	[101]
Leukemia	*KIR2DL1; KIR2DL2; KIR2DL3*	Susceptibility	[103]
Hodgkin's lymphoma	*KIR2DS1; KIR3DS1*	Protection	[106]
Nasopharyngeal carcinoma	≥5 activating *KIR*	Susceptibility	[108]
Cervical Cancer	*KIR3DS1*and absence of *HLA-C2 &/or HLA-Bw4*	Susceptibility	[107]
T-LGL	Expression of inhibitory KIR in absence of ligands	More severe disease	[112]
NK-LGL	Expression of activating KIR	May contribute to disease pathogenesis	[111,
Sezary syndrome	Expression of KIR3DL2	Useful diagnostic marker	[110]

Disease	KIR-HLA ligand pair	Effect	Ref.
REPRODUCTION			
Preeclampsia	Mothers with AA *KIR* genotype; fetus with *HLA-C2*	Susceptibility	[117]
Recurrent miscarriages/spontaneous abortions	Lack of *KIR2DS1* in mothers and increased frequency of *HLA-C2* in both mother and male partner	Susceptibility	[120]
	Increased *KIR2DS2* and decreased *HLA-C2* frequency, overall increased frequency of activating *KIR.*	Susceptibility	[121]
	Higher cell surface expression of KIR2DL4	Susceptibility	[122]