Review Article

Killer Cell Immunoglobulin-Like Receptors Influence the Innate and Adaptive Immune Responses

Raja Rajalingam

UCLA Immunogenetics Center, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California at Los Angeles, 1000 Veteran Avenue, Room# 1-536 Box: 951652, Los Angeles, CA 90095-1652, Tel: 310 825 1467, Fax: 310 206 3216, e-mail: rrajalingam@mednet.ucla.edu

ABSTRACT

Natural killer (NK) cells are a subset of lymphocytes which play a crucial role in early innate immune response against infection and tumor transformation. Furthermore, they secrete interferon-γ (IFN-γ) and tumor necrosis factor (TNF) prompting adaptive immunity. NK cells distinguish the unhealthy cells from the healthy ones through an array of cell-surface receptors. Human NK cells use inhibitory and activating killer cell Ig-like receptors (KIR) as primary probe to discriminate between healthy and unhealthy cells. The inhibitory KIRs recognize HLA class I molecules and trigger signals that stop NK killing. The activating KIRs are believed to recognize the determinants associated with infections and tumors, and trigger signals that activate NK killing. Therefore, the effector function of a given NK cell depends upon the receptors that it expresses and ligands that it recognizes on the targets. Genes encoding KIRs and HLA ligands are located on different chromosomes, and vary in number and type. The independent segregation of KIR and HLA genes results in variable KIR-HLA combinations in individuals, which may determine the individual's immunity and susceptibility to disease.

Keywords: NK Cells, Innate Immunity, HLA, KIR, Polymorphism

NATURAL KILLER (NK) CELLS

NK cells were initially defined as large granular lymphocytes that kill tumor cells without prior sensitization (1). Using the nonadaptive and non-MHC restricted cell-mediated "natural" cytotoxicity, the NK cells mediate first-line of defense against invading pathogens and tumor growth (2- 4). Currently, the NK cells are defined as the $CD3^-$ $CD56^+$ subset of lymphocytes, and they comprise approximately 10 to 20% of the mononuclear cell fraction in normal peripheral blood. NK cells share several common features with CD8+ cytotoxic T lymphocytes (CTL) in their development, morphology, cell-surface phenotypes, killing mechanism (i.e., using perforin and granzymes), and cytokine production such as interferon-γ (IFN-γ) and tumor necrosis factor (TNF) (5, 6). Despite several similarities, NK cells and CTLs differ in timing and stamina of the immune response: the NK cells act within hours of infection but lack endurance, whereas the CTLs need several days to arise but sustain for life. Another important distinction is that the NK cells are unable to produce IL-2. Furthermore, the CTLs and NK cells differ in receptors used to sense the unhealthy target cells. The CTLs use clonally restricted T cell receptors (TCR), which are generated by gene rearrangement. The TCR recognizes the foreign peptides loaded in the context of self-HLA class I molecules, and triggers positive signals that activate T cells against the affected unhealthy cells. Contrarily, the NK cells use a variety of germline-encoded non-arranging receptors with either inhibitory or activating functions (7- 10). The inhibitory receptors recognize self-HLA class I molecules while the activating receptors recognize the non-self molecules associated with infection and tumor transformation. The net signal integrated from the inhibitory and activating receptors determines the effector function of NK cells (7). Several distinct gene families encode inhibitory and activating receptors for NK cells (11, 12). This review focuses on killer cell immunoglobulin-like receptors (KIR), a family of polymorphic key receptors that regulate human NK cell function in distinguishing unhealthy targets from the healthy-self (12- 16).

KILLER CELL IMMUNOGLOBULIN-LIKE RECEPTORS (KIR)

Fourteen distinct KIR receptors have been identified in humans (Figure 1). They comprised of either two or three extracellular immunoglobulin-like domains that form ligand-binding segments and either a long or short cytoplasmic tail involved in signal transduction. The names given to the KIR genes are based on the structures of the molecules they encode (17). The first digit following the KIR acronym corresponds to the number of Ig-like domains in the molecule and the 'D' denotes 'domain'. The D is followed by either an 'L' indicating a 'Long' cytoplasmic tail, an 'S' indicating a 'Short' cytoplasmic tail or a 'P' for pseudogenes. The final digit indicates the number of the gene encoding a protein with this structure. Thus KIR2DL1, KIR2DL2 and KIR2DL3 all encode receptors having two extracellular Ig-like domains and a long cytoplasmic tail. The long-tails include one or two immune-receptor tyrosine-based inhibitory motifs (ITIM), which trigger inhibitory signals. The short tails do not carry any signaling motifs. The receptors with a short tail carry a charged amino acid residue in their transmembrane region, which allow these receptors to bind to the adopter molecules like DAP10 and DAP12 (18). These adopter chains contain immune-receptor tyrosine-based

activation motifs (ITAM), which trigger activating signals upon binding of the short-tailed KIR receptor to a relevant ligand.

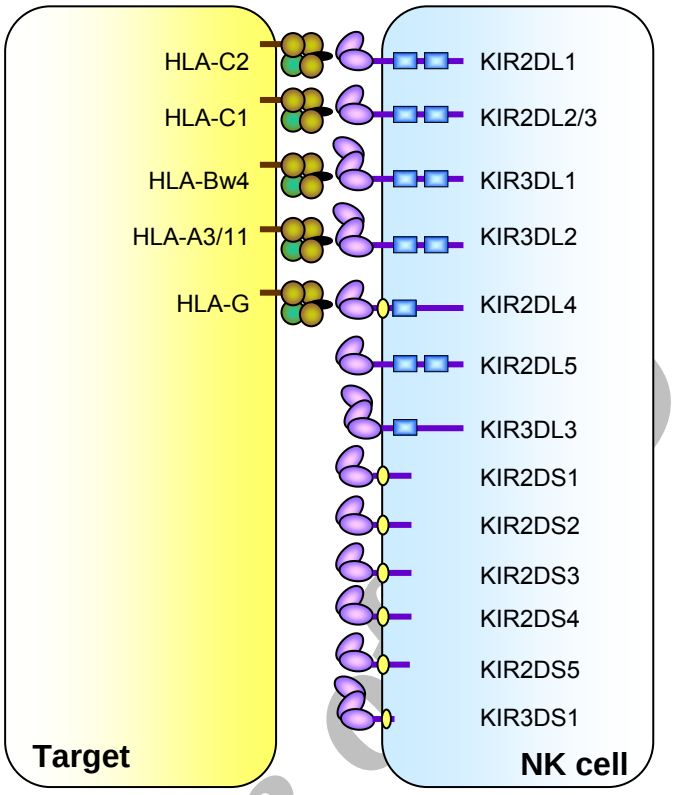

Figure 1. Killer cell Immunoglobulin-like Receptors (KIR). Fourteen distinct KIR receptors have been characterized in humans that comprise either 2 or 3 (2D or 3D) extracellular Ig-like domains and either a long (L) or short (S) cytoplasmic tail. Six KIR receptors are activating types and the remaining KIR are inhibitory types. The ITIM motifs in the cytoplasmic tails of iKIRs are shown as boxes, and positively charged residues in the transmembrane regions of aKIRs are shown as circles. The iKIR receptors bind to distinct HLA class I allotypes and the ligands for the aKIR receptors not known.

The inhibitory KIRs (iKIR) recognize a distinct motif of polymorphic HLA class I molecules and trigger signals that restrain NK cell action (Figure 1). Therefore, by expressing HLA-A, B, and C molecules, the healthy cells become resistant to NK surveillance. Downregulation of HLA class I expression due to tumor transformation or viral infection relieves the inhibitory influence on NK cells, permitting NK cells to lyse these unhealthy target cells, a phenomenon first described as the `missing-self' hypothesis (19, 20). The following iKIR-HLA class I interactions have been well defined: KIR2DL1 binds to Cw*0201, Cw*0401, Cw*0501, Cw*0601 and Cw*1503 allotypes having lysine at amino acid position 80 located in the F-pocket of the peptide binding groove (HLA-C^{K80} --- termed the C2 group) (21-23). KIR2DL2 and 2DL3 bind the remaining HLA-C allotypes (Cw*0102, Cw*0304, Cw*0702 and Cw*08) with asparagine at position 80 (HLA-C^{N80} -- termed the C1 group). The inhibitory signals triggered by the KIR2DL2/3+HLA-C1 interaction is relatively weaker as compared to those triggered by the KIR2DL1+HLA-C2 interaction (24). KIR3DL1 binds to Bw4, a serologically defined public epitope (residues 77-83 on α1 domain) that presents on

40% of the HLA-B allotypes and certain HLA-A allotypes (HLA-A23, 24, 25 and 32) (25- 27). KIR3DL2 recognizes HLA-A3 and A11 allotypes (28, 29). The strength of these specific iKIR-HLA class I interactions are highly sensitive to the HLA class I bound peptide sequence (24, 27, 30- 34). The KIR2DL4 receptor binds to the trophoblast-specific non-classical class I molecule HLA-G and induces rapid IFN-γ production that promotes vascularization of the maternal decidua during early pregnancy (35- 38). In addition to its activation function, the KIR2DL4 receptor carries a single ITIM motif in its cytoplasmic tail and exhibits inhibitory function (39- 41). Although the cell-surface expression of two other inhibitory receptors KIR3DL3 and 2DL5 was recently confirmed (42, 43), the ligands for these receptors have yet to be discovered.

The ligands for the activating KIRs (aKIR) are unknown or uncertain. Certain aKIRs are predicted to bind to the same HLA class I ligands as their structurally related iKIRs. For instance, 3DS1 that shares the highest sequence homologies with 3DL1 in their extracellular Ig-domain is believed to bind to HLA-Bw4 (44). Similarly, 2DS1 (homologue of 2DL1) and 2DS2 (homologue of 2DL2) are considered to bind to HLA-C2 and HLA-C1 allotypes, respectively. Consistent with these predictions, soluble KIR2DS1-Fc was shown to bind weakly to HLA-C2 (45). Furthermore, tetramer-based cellular assays and direct affinity measurements revealed that the strength of this interaction is sensitive to the bound peptide sequence (46). Taken as a whole, the KIR-HLA interaction depends on polymorphism of KIR and HLA genes as well as the HLA-bound peptides.

NK CELLS EXPRESS A VARIABLE KIR RECEPTOR REPERTOIRE

The number and type of KIR receptors are substantially variable between individuals. The NK cells within a given individual can express variable number and type of KIR receptors. The genetic and transcriptional factors contributing to the KIR receptor repertoire diversity are discussed here:

1. Variable Gene Content of KIR Haplotypes. The KIR genes are located in the leukocyte receptor complex (LRC) that spans a region of about 150 kb on chromosome 19q13.4 (47- 49). The number and type of KIR genes arranged on the haplotypes differ substantially, a property previously described for HLA-DRB haplotypes (Figure 2). The most frequently occurring KIR haplotype in humans is relatively simple, and carries a fixed number of 9 genes (6 iKIR genes, 1 aKIR gene and 2 pseudogenes). This haplotype is commonly referred to as the group-A KIR haplotype (50). The other KIR haplotypes comprise more than one aKIR gene and are referred as group-B haplotypes (51, 52). The gene content of group-B haplotypes varies dramatically by haplotype (51, 52). Even more complicated haplotypes have been identified with two copies of a gene on the same haplotype (53- 56). Only three KIR genes (KIR2DL4, 3DL2 and 3DL3) are present invariably on all KIR haplotypes and they are referred to as `frame-work´ genes (48). Segregation of different group-A and group-B haplotypes generates human diversity in the numbers and types of KIR genes they inherit (genotypes). For example, homozygotes for group-A haplotypes have only seven functional KIR genes, whereas heterozygotes for group-A and group-B haplotypes may have all 14 functional KIR genes.

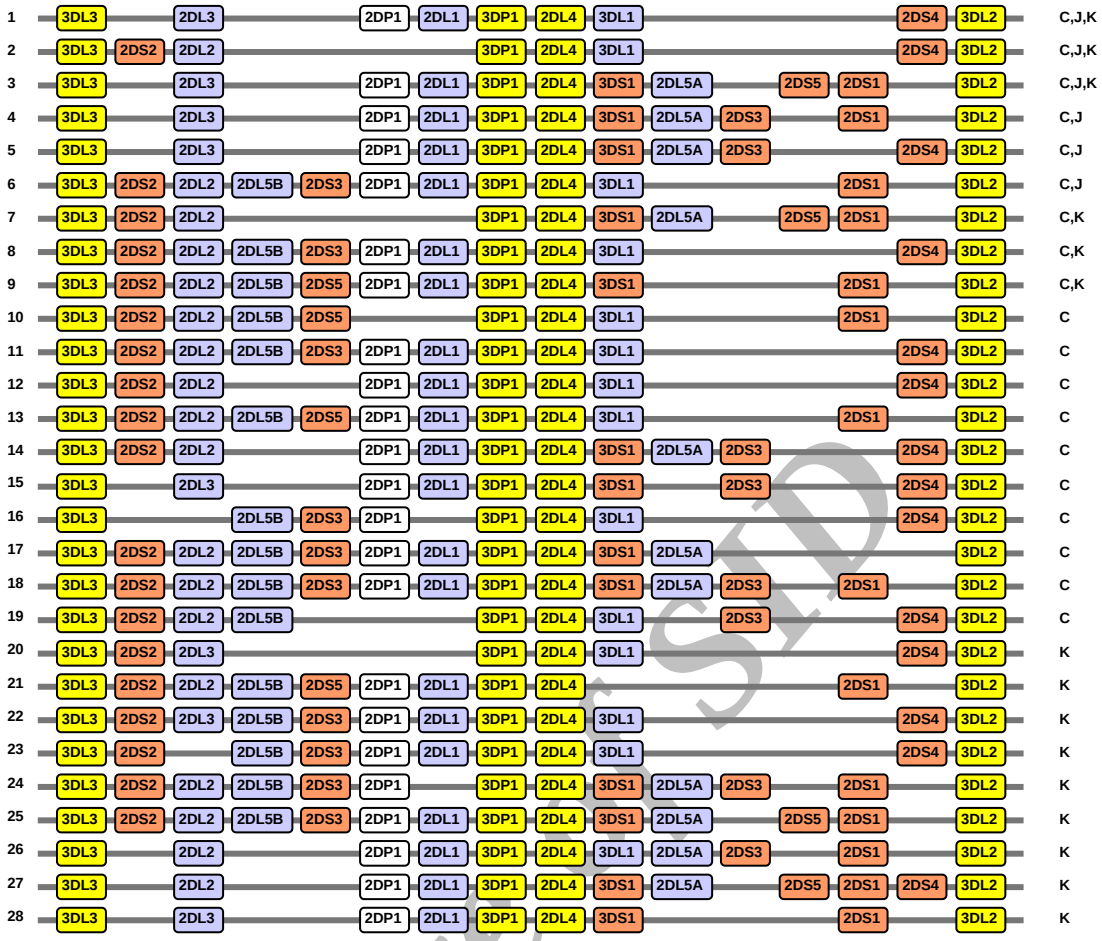

Figure 2. KIR haplotypes have variable gene content. Map of KIR haplotypes as determined by family segregation analyses (51, 52, 58, 73, 78). Haplotype 1 represents group-A KIR haplotype and the remainder group-B haplotypes. The ethnic populations in which each haplotype was characterized are indicated as C, J and K representing Caucasian, Japanese, and Korean, respectively. Maps are not drawn to scale.

Genotyping studies revealed a significant ethnic difference in the distribution of KIR genotypes (Figure 3) (57- 73). Over 50% of Caucasians are homozygous for group-A haplotypes (Figure 3, genotype#1), which comprise just one activating KIR2DS4 gene (11, 50, 52, 57, 61, 63). In contrast, the populations of the Indian subcontinent and Australian aborigines carry a dominant group-B KIR haplotypes (60, 67, 68). NK cells of group-B haplotypic individuals express more activating NK receptors and respond more vigorously to pathogens. It is likely that group-B haplotypes were positively selected by nature over time in certain Asian populations to survive in pathogen rich environment.

Genotypes #	KIR Genes																% Frequencies								
	2DL1	2DL2	2DL3	2DL4	2DL5	3DL1	3DL2	3DL3	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	2DP1	3DP1	Caucasian (n=812)	African (n=328)	Chinese Han (n=104)	Korean (n=154)	Japanese (n=132)	Vietnamese (n=59)	Thai (n=119)	Asian Indian (n=258)	Aus. Aborigine (n=67)
1																	30.6	32.0	58.7	55.2	56.0	42.4	35.4	10.6	1.7
2																	11.9	4.4	12.4	15.8	19.5	8.5	4.2	5.2	4.5
3																	11.7	6.3	5.7	4.7	4.8		11.8	6.7	
4																	5.8	2.0	3.8	4.7			3.4	1.3	
5																	5.4	0.5		0.6		3.4	4.2	2.0	14.9
6																	4.1	13.3		0.6	2.5	5.1	3.4	8.8	4.5
7																	3.9	0.9	1.0	0.6			3.4	6.3	
8																	3.4			1.3			1.7	4.1	
9																	2.0	0.5	1.9		4.8			0.5	
10																	1.6							0.5	
11																	1.3	0.2	1.0						
12																	1.2	1.7	1.0	0.6			0.8	3.4	
13																	1.2		1.0				3.4		
14																	1.1	0.4					0.8		
15																	1.0	2.1						2.0	
16																	1.0	0.4	5.7	7.9	7.4		4.2	0.7	
17																	0.8		1.0	0.6	2.5		1.7		
18																	0.6						2.5	0.9	
19																	0.6	0.4						1.7	
20																	0.5							2.1	
21																	0.5								
22																	0.5								
23																	0.5						1.7	1.0	
24																	0.4								
25																	0.4			1.3			1.7	3.0	
26																	0.3							0.5	
27																	0.3	0.9							
28																	0.3		1.0						
29					nt										nt	nt	0.3						4.2		
30																	0.3	0.4						0.5	
31					nt										nt	nt	0.3								
32					nt										nt	nt	0.3						0.8		
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37																	0.2	0.4						1.0	
38																	0.2							0.5	
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42					nt										nt	nt	0.2								
43					nt			nt					nt		nt	nt	0.2								
44					nt										nt	nt	0.2					5.1			14.9
45																	0.2								
46																	0.2		1.9	0.6			1.7	1.7	
47																	0.2								
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56															nt	nt	0.1							1.0	
57					nt			nt					nt		nt	nt	0.1								
58					nt										nt	nt	0.1						0.8		
59					nt			nt					nt		nt	nt	0.1								
60																	0.1		1.0	1.9			0.8	0.7	
61																	0.1								
62					nt										nt	nt	0.1								22.4
63																	0.1								
64																	0.1								
65																	0.1								
66																	0.1	1.3							
67					nt										nt	nt	0.1								
68																	0.1	0.4						0.3	

Figure 3. Frequency of KIR genotypes in ethnic populations. Genotyping studies revealed a significant ethnic difference in the distribution of KIR genotypes. The KIR genotypes that differ from each other by the presence (shaded box) and absence (white box) of 16 KIR genes. The frequency of each genotype is expressed as a percentage and defined as the number of individuals having the genotype divided by the number of individuals studied in the population group. The data was extracted from the following studies: Caucasian (61, 63, 64, 66), African (64, 67), Chinese Han (59), Korean (58), Japanese (160), Vietnamese (60), Thai (61), Asian Indians (64, 67, 68), and Australian Aborigines (60).

2. Nucleotide Polymorphism of KIR Genes. In addition to haplotypic diversity, each KIR gene exhibits considerable allelic diversity (17, 72, 74- 76). The highest allelic polymorphism was observed with 3DL1 comprising over 40 variants (Figure 4). The framework genes 2DL4, 3DL2 and 3DL3 comprise over 20 alleles each. Other KIR genes are relatively conserved. The amino acid substitutions that distinguish allelic diversity of 3DL1 is shown to be rich in the region the receptor contacts the polymorphic HLA-Bw4 ligands (77). The sequence polymorphism of KIR3DL1 is shown to influence their expression, ligand binding and cytolytic and cytokine secretion functions (24, 77- 81). Some nucleotide mutations affect the cell-surface expression of KIR receptors. For example, chain-terminating frame-shift deletions were reported for KIR2DS4 (51, 82) and 2DL4 (83- 85). Similarly, sequence variation in the promoter region is associated with the lack of 2DL5 expression (86) and amino acid polymorphism is largely responsible for the intracellular retention of 3DL1*004 (87) and 2DL2*004 (79). The synergistic combination of allelic polymorphism and variable gene content individualize KIR genotypes to an extent where unrelated individuals almost always have different KIR types (74). This level of diversity likely reflects a strong pressure from pathogens on the human NK cell response.

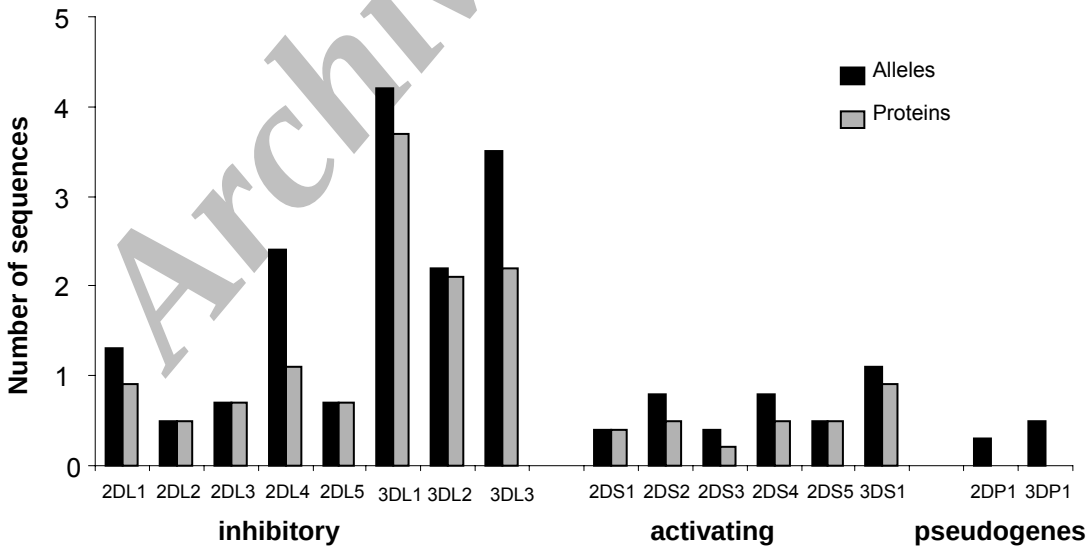

Figure 4. Allelic polymorphism of KIR genes. The number of sequences identified for each KIR gene is shown. The statistics were obtained from the IPD-KIR database, release 1.2.0, November 2006 (http://www.ebi.ac.uk/ipd/kir/index.html).

3. Transcriptional Variation of KIR Genes. The level of mRNA expression varies between KIR genes. For example, the KIR3DL3 transcripts are detected at low levels in peripheral blood as compared to other KIR genes (14). The current hypotheses explaining variegated expression of KIR genes are based on the methylation state of active versus silent KIR alleles (88- 90). Further, alternatively spliced mRNA are reported for most KIR genes, and such isoforms can affect the cell surface expression and ligand binding (91).

4. Clonal Diversity of KIR Cell Surface Expression. KIR receptors are clonally expressed. NK cells within an individual can express different number and combinations of KIR receptors. The majority of NK cells in peripheral blood express at least one inhibitory receptor for self-MHC class I and is functionally competent to recognize and eliminate target cells that have down-regulated the respective MHC class I ligands (10, 92). Additionally, a subpopulation of developmentally immature NK cells exists that lacks inhibitory receptors for self-MHC class I and is generally hyporesponsive to target cells that are deficient in MHC class I expression (93- 95). In this regard, it was recently shown that the acquisition of functional competence, a process called "licensing," is mediated through interaction of inhibitory NK cell receptors with cognate class I ligands (94, 96, 97). Therefore, it appears that a minimum of one iKIR-HLA interaction is crucial for the development of functional NK cells. Consistent with this, the NK cells from MHC-deficient mice and humans were shown to be defective in target killing (98, 99). The NK cell receptor repertoire is very different from those expressed on T cells. The T cells express only the activating type of TCR that is specific to just a single HLA molecule and bound peptide. On the other hand, the NK cells express multiple inhibitory and activating KIR receptors for different ligand specificities, and their action depends upon the balance between these distinct signals.

Two subsets of NK cells in peripheral blood have been recognized (100). The majority belong to the $CD56^{dim}$ subset, which expresses moderate levels of CD56 and high levels of CD16. The $CD56^{dim}$ NK cells usually express KIR and are heterogeneous with respect to the expression of killer cell lectin-like receptors (KLR). The minor subset of NK cells are the $CD56^{bright}$ phenotype that accounts for only 10% of circulating NK cells. These cells express high levels of CD56 and KLR, and tend to lack expression of CD16 and KIRs. The two subsets of NK cells differ also in terms of chemokine receptor and adhesion molecule expression, suggesting that they have different homing properties (101). Indeed, the $CD56^{bright}$ cells have been found to be the dominant NK cell subset in human lymph nodes (102). Furthermore, they show important functional differences; the $CD56^{dim}$ subset has superior cytotoxic capacity, whereas the $CD56^{bright}$ subset has greater ability to produce proinflammatory cytokines on exposure to low concentrations of monokines (103). Recently, a great expansion of the $CD56^{bright}$ subset of NK cells was demonstrated in synovial fluid of patients with inflammatory arthritis (104). These NK cells, a subset of the innate immune system, are therefore well positioned to engage in positive feedback within the cytokine networks and to contribute to the persistence of inflammation in autoimmune joint disease.

KIR GENES ARE RECENTLY ORIGINATED AND RAPIDLY EVOLVING

Three distinct families of MHC class I specific receptors that could control NK function have been characterized: KIR receptors, Ly49 receptors, and CD94:NKG2 receptors

(105) (Figure 5). Only the CD94:NKG2 family is used by both human and mouse NK cells, and these genes are highly conserved between these two species showing 60-80% nucleotide homologies (106, 107). Genes encoding Ly49 and CD94:NKG2 receptors belong to the NK gene complex (NKC) located on chromosome 12 in humans and chromosome 6 in mouse (108). Ly49 are the key mouse NK cell receptors encoded by 15-20 polymorphic genes (109). In humans, the Ly49 family has been reduced to a single unexpressed pseudogene (110, 111). On the other hand, humans use KIR receptors as major class I specific NK cell receptors. In mice, only two KIR-like genes have been identified on the X-chromosome (112). However, the expression and NK cell function of these mouse molecules are not defined. This species comparison suggests that the KIR system originated recently after the divergence of human and mouse lineages, which occurred around 65 million years ago (113).

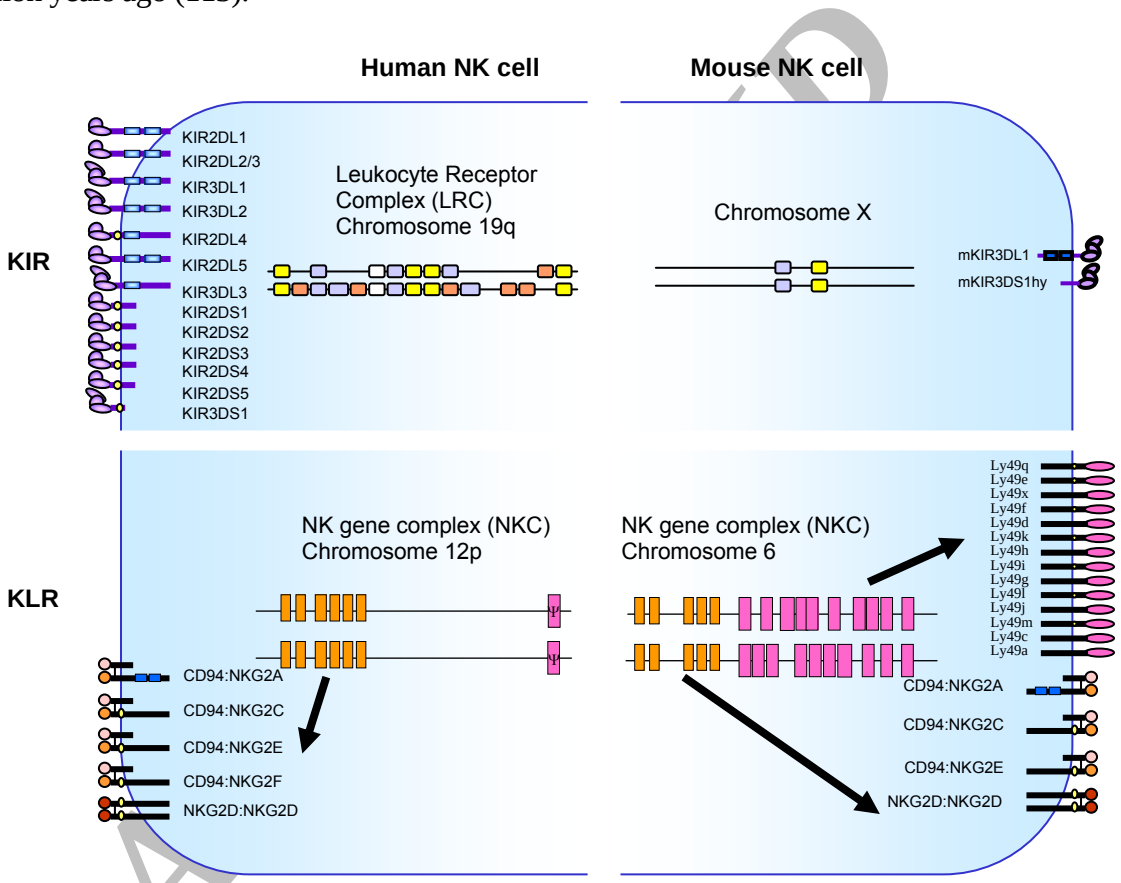

Figure 5. Human and mouse NK cells use distinct families of MHC class I-specific receptors. The CD94:NKG2 family of NK receptors are used by both human and mouse NK cells. Ly49 receptors are exclusively used by mouse NK cells, which are reduced to a single pseudogene in humans. The humans use KIR receptors as major class I specific NK cell receptors, which is under developed in the mouse.

The chimpanzee and gorilla are the closest living relatives to humans. Their common ancestor is estimated to have existed around 5-8 million years ago (114). The chimpanzees and gorillas share >98% homology with humans in their general genome (115). Further, the MHC class I genes in these apes are the direct counterparts (orthologs) to human HLA-A, B and C genes. However, only three KIR genes are conserved among

humans, chimpanzees and gorillas (116- 118). Most chimpanzee and gorilla KIR genes have diverged to the point where the orthologous relationships with human KIRs are lost. These findings suggest that the KIR genes are a rapidly evolving system, and the driving force of this dynamic evolution is not restricted to the polymorphic MHC class I genes. The nature of rapid evolution could potentially contribute to KIR diversity within and between species.

KIR RECEPTORS CAN CONTROL T CELL FUNCTION

In addition to NK cells, KIR receptors are expressed on a subset of $CD8^+$ T cells with a memory phenotype indicating that the KIRs can regulate the antigen-specific T cell immune response, affirming their role in adaptive immunity (119- 121). Similar to NK cells, HLA class I-specific inhibitory receptors might subserve on T cells an important negative control that participates in the prevention of autologous damage. Furthermore, recognition of HLA class I molecules by iKIR receptors on T cells down-regulate the activation-induced cell death, and promotes the survival of CD8+ memory T cells (122). The majority of CD4 T cells constitutively expresses the CD28 molecule, a key player in providing co-stimulatory signals to induce T cell activation and to prevent T cell apoptosis (123). CD4 T cells lacking the CD28 molecule are distinctly infrequent in most normal individuals (comprising 0.1–2.5% of T cells) (124). However, $CD4+CD28^{null}$ cells are expanded in RA patients expressing variable KIR receptors (125). Particularly, a preponderance of aKIR receptors on $CD4+CD28^{null}$ T cells and their co-stimulatory function on these CD28 negative T cells prompted the hypothesis that the aKIR receptors may predispose a person to autoimmune manifestation (126- 128).

HUMAN LEUKOCYTE ANTIGENS (HLA)

The HLA proteins are encoded by a fascinating genetic region located in the major histocompatibility complex (MHC) (129). The human MHC comprises about 3.6 Mb DNA located on the short arm of chromosome 6 (6p21.3). The MHC is the most gene-dense region of the human genome containing 224 identified loci (130). Nearly 40% of the expressed MHC genes in humans have immune-related function. The HLA genes in the human MHC encodes cell-surface glycoproteins displaying a remarkable degree of polymorphism (131, 132). The differences among HLA proteins are localized primarily to the amino terminal region of these molecules, which bind peptides and interact with T-cell receptors or KIR receptor molecules. The extensive allelic diversity at these loci is generated by point mutations, recombinations, and gene conversions. Rapidly evolving viruses and pathogens drive HLA polymorphism, and consequently the presence of iKIR-binding HLA motifs (A3/11, Bw4, C1 and C2) are variable in individuals (132- 134).

HUMAN DIVERSITY IN KIR-HLA COMPOUND GENOTYPES

Given that KIR genes at chromosome 19q13.4 and HLA genes at chromosome 6p21.3 are polymorphic and display significant variations, the independent segregation of these unlinked gene families produce diversity in the number and type of KIR-HLA pairs inherited in individuals (65). Individuals carrying homozygous group-A KIR genotypes (AA genotypes) are frequent (30-58%) in most ethnic populations (Figure 3, Genotype#1). The exceptions are the Asian Indians and Australian aboriginals, in which the individuals carrying AB and BB genotypes are frequent. The NK cells from the AA homozygous individuals can express a maximum of four iKIR receptors (2DL1, 2DL3, 3DL1 and 3DL2) and one activating KIR2DS4 receptor (Figure 6). In contrast, the individuals carrying AB or BB KIR genotypes can express a maximum of five iKIR receptors (2DL1, 2DL2/3, 2DL5, 3DL1, and 3DL2) and 2 to 6 aKIR receptors. The function of the iKIR receptors depends on the availability of their specific cognate HLA class I ligands. Only a few individuals carry cognate HLA class I ligands for all iKIR receptors, but most individuals carry ligands for 2 to 3 iKIR receptors (65). Around 20% of the population carries a single iKIR-HLA pair (Figure 6, KIR-HLA compound genotypes 1 & 3). Since the KIR receptors are clonally expressed on NK cells in a stochastic manner such that each NK cell clone expresses only a portion of the genes within the gene profile, a substantial fraction of circulating NK cells of individuals with a single iKIR-HLA pair may not express iKIR to the self-HLA class I molecules (10, 92), and the NK cells lacking the iKIR expression may trigger autoreactivity on stressed-self tissues with further development of a systemic autoimmune condition. Furthermore, the environmental insults affecting HLA class I expression could promote the break down of self-tolerance and trigger autoimmunity in individuals carrying just one inhibitory iKIR-HLA combination.

The presence of the cognate HLA class I ligand increases the frequency of NK cells expressing the specific iKIR receptor (78). Therefore, the majority of the NK cells from an individual carrying more than one iKIR-HLA pair is predicted to express multiple iKIR receptors that mediate strong inhibition, and consequently less susceptibility to autoimmunity (Figure 6, KIR-HLA compound genotypes 2 & 4). On the other hand, excessive inhibitory signals triggered through multiple iKIR-HLA interactions may have a detrimental effect by blocking the effector function of NK cells against pathogens and malignant tissues.

Although the cell surface expression and ligands for the aKIR receptors have not been defined, a series of genetic epidemiological data have revealed the association of distinct aKIR in antiviral immunity (44, 135), autoimmune diseases (136- 139) and cancer progression (140, 141). In these models, the activation signals were believed to overcome HLA-dependent inhibition (7). Genotypes encoding a dominant inhibitory KIR receptor repertoire (iKIR+HLA>aKIR) are likely protective against autoimmunity but susceptible for infection and tumor (Figure 6, KIR-HLA compound genotype 2). Genotypes encoding a dominant activating KIR receptor repertoire (iKIR+HLA<aKIR) are presumably susceptible to autoimmunity but instrumental in antiviral and anti-tumor immunity (Figure 6, KIR-HLA compound genotype 3).

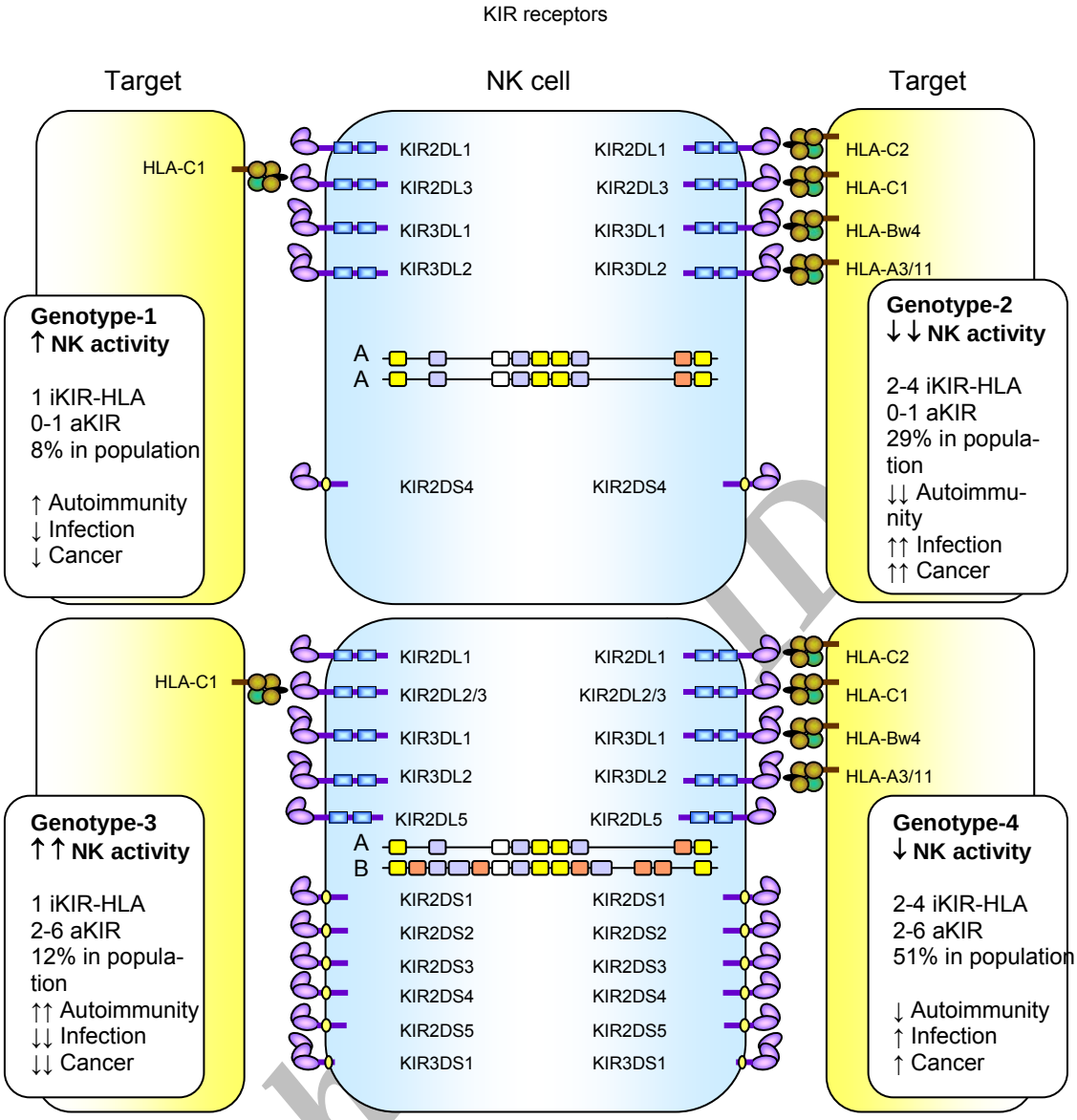

Figure 6. Model depicting the contribution of KIR-HLA compound genotypes in human diseases. Predominant inhibitory KIR-HLA ligand combinations with fewer aKIR receptors suppress the NK and NK-like T cells, and maintain the tolerance to self. In contrast, the predominant aKIR receptors and fewer inhibitory KIR-HLA ligand combinations may activate the NK and NK-like T cells, and breakdown the self-tolerance leading to autoimmunity.

KIR-HLA IN HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT)

Allogeneic (genetically different) HCT is an effective therapy for an increasing number of life-threatening hematological, oncological, hereditary and immunological diseases (142- 144). During HCT therapy, the entire hematopoietic system of the patient is destroyed using a severe conditioning regimen and reconstituted by the infusion of pluripotent stem cells from a donor (145, 146). HCT is accompanied by reciprocal immunological reactions of the graft against its new host and the host against the graft. Immunocompetent cells transplanted with the stem cells or arising from them exert Graft-versus-tumor effect (GVT), which is a remarkable alloreactivity against host's tumor. Unfortunately, alloreactive donor cells also mediate graft-versus-host disease (GVHD), which lethally

attacks the host's tissues particularly those that have been stressed by the pre-transplant conditioning regimen (i.e., skin, liver and intestine). The residual host immunocompetent cells that survive the conditioning regimen may mount an immunological attack against the graft, leading to graft rejection (host-versus-graft effect, HVG).

Donor-derived T cells in the stem cell preparations are potential immunocompetent cells, which will confront the mismatched HLA molecules of the recipient and react vigorously causing GVHD and GVT. Matching of HLA between donor and recipient reduces the T cell alloreactions (147- 149). In HLA identical transplantations, such as autologous transplantation, transplantation between the genetically identical twins or between HLA-identical siblings, the incidence of GVHD as well as GVT is decreased. However, less than one third of eligible patients have an HLA-identical sibling donor. To overcome this limitation, the transplantation from matched unrelated donors (MUD) are performed using international registries of HLA-typed individuals (150, 151). Generally, patients undergoing MUD-HCT, compared to those receiving sibling-HCT, display a higher incidence of GVHD, suggesting the role of non-T cell-mediated mechanism(s) involved in GVHD and GVT (152- 154). Studies with mice suggest the role of NK alloreactivity in bone marrow transplant rejection (155- 157). Recent studies with HLA-haploidentical transplantation revealed a potential role of NK cells in mediating enhanced anti-leukemic effect, decreased GVHD, and survival advantage of allogeneic HCT (158, 159).

Following allogeneic HCT, the recipient reconstitutes NK cells from the donor stem cell graft, and thereby the donor NK receptor and recipient HLA class I ligand determines the functional ability of the reconstituted NK cells. The central hypothesis is that patients reconstituted with more inhibitory `receptor-ligand´ combinations develop a lower degree of GVHD, and patients reconstituted with more activating receptors show a high GVT effect. The donor graft from group-A homozygotes develops NK cells expressing four iKIRs and one or no aKIR (Figure 6). The alloreactivity of these donor NK cells depends on the recipient's HLA type. If the recipient expresses most of the HLA class I ligands (HLA-C1, C2, Bw4, and A3/11), the donor NK cells are likely inhibited and become tolerant to recipient tissue, so that less or no GVHD will result. In contrast, recipients lacking these HLA ligands fail to inhibit all donor NK cells and result in NK mediated GVHD. Since the group-A homozygotes express just one or no aKIR, these NK cells may poorly recognize tumors, and thus low GVT effect is expected. The grafts from AB or BB haplotypic donors develop NK cells expressing more than one aKIR in addition to 4 to 6 iKIRs. The iKIRs will recognize relevant HLA ligands on recipient tissues and stop NK alloreactivity. The aKIRs will presumably recognize and kill recipient tumors leading to an increased GVT effect. If the recipient does not have ligands for all iKIRs, the GVHD effect is increased. In summary, the degree of KIR-HLA interactions may determine the success rate of haematopoietic cell replacement therapy for certain leukemias.

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