Understanding how combinations of HLA and KIR genes influence disease

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Combinations of HLA and killer cell immunoglobulin–like receptor (KIR) genes have been associated with diseases as diverse as autoimmunity, viral infections, reproductive failure, and now cancer. Much as early observations of disease associations with HLA polymorphism preceded a detailed knowledge of HLA recognition by T cell receptors, the recently reported disease associations with HLA–KIR gene combinations beg for a better understanding of the underlying mechanisms.

KIRs and ligands

Natural killer (NK) cells are regulated in part by inhibitory receptors that recognize MHC class I molecules on normal cells. In humans, inhibitory receptors that recognize classical MHC class I molecules (HLA-A, HLA-B, and HLA-C) belong to the KIR family. KIRs are a family of ~15 closely linked genes located on chromosome 19q13.4, which encode both inhibitory and activating receptors that are expressed by NK cells and by subsets of $\gamma\delta^+$ T cells and memory and effector $\alpha\beta^+$ T cells. The reason for KIR diversity and the contribution of individual KIRs to signaling in NK cells and T cells are not fully understood, but their importance has been underscored by several recent genetic studies, including one in this issue (1), which have linked combinations of KIR and HLA genes with the outcome of various diseases (Table I) (2–8). Associations with different HLA–KIR combinations, involving activating KIRs or inhibitory KIRs to different extents, have been described. The data suggest that disease can be modified by specific KIR–ligand interactions, rather than by global responsiveness of NK cells or T cells.

KIRs contain either two or three immunoglobulin-like domains with either long (2DL, 3DL) or short (2DS, 3DS) cytoplasmic tails (Table II) (9). Long-tailed receptors carry one or two immunoreceptor tyrosine-based inhibition motifs (ITIMs), which contribute to inhibitory signaling. Short-tailed receptors have a lysine residue in their transmembrane domain that is required for pairing with the immunoreceptor tyrosine-based activation motif (ITAM)–containing adaptor DAP12. Several inhibitory KIRs have well-defined MHC class I ligands (Table II) (10, 11). The ligands for activating KIRs, however, have been more elusive. Despite high sequence similarity with some of the inhibitory receptors, activating KIRs show either weak or undetectable binding to HLA class I (12–14).

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KIR genotypes and disease

A striking feature of KIR genes is their lack of conservation among species and their rapid evolution, which cannot be accounted for solely by divergence in HLA class I molecules (15). If KIR gene evolution were pathogen driven, some of the diversity would be expected to correlate with resistance or sensitivity to certain infectious diseases. Indeed, several genetic studies of viral infection have revealed an influence of HLA–KIR gene interactions on disease outcome (Table I). An interaction between *KIR3DS1* and a subset of *HLA-Bw4* alleles—those with Ile at position 80—is associated with delayed progression to AIDS in HIV-infected individuals (2). In the case of hepatitis C virus (HCV) infection, homozygosity of both *HLA-C1* and *KIR2DL3* is associated with resolution of infection (4). A hypothesis proposed to explain the latter finding is that KIR2DL3 binds HLA-C with lower affinity than KIR2DL1 and KIR2DL2 receptors, thus reducing NK cell inhibition and favoring resolution of the infection. However, direct affinity measurements have not revealed a difference between KIR2DL binding to their respective HLA-C ligands (Table II). The report in this issue (1) reveals a predisposition to human papilloma virus (HPV)–induced cervical cancer with HLA–KIR gene combinations that seem to favor NK cell activation. In contrast to correlations seen with HIV and HCV infections, disease progression toward cervical neoplasia seems enhanced by an increase in activation signals.

Combinations of certain HLA–KIR genotypes have also been linked with susceptibility to autoimmune diseases. Thus, a combination of *KIR2DS1* and/or *KIR2DS2* coupled with homozygosity of an HLA-C group favors susceptibility to psoriatic arthritis (5). Susceptibility could be due to reduced NK cell inhibition, as individuals homozygous for *HLA-C1* lack a ligand for KIR2DL2 and KIR2DL3, and those homozygous for *HLA-C2* lack a ligand for KIR2DL1. Similarly, *KIR2DS2* combined with *HLA-C1* in the absence of *HLA-C2* and *HLA-Bw4* is associated with increased susceptibility to type I diabetes (3). Likewise, *KIR2DS1* in combination with *HLA-Cw*06* is a risk factor for psoriasis vulgaris (7). HLA–KIR combinations that favor NK cell or T cell activation may have been selected to improve resistance to viruses and to malignancy (8), despite an associated risk of developing autoimmunity (Table I).

HLA–KIR gene combinations that seem to favor NK cell inhibition have also been associated with preeclampsia

Table I. Disease associations with combinations of KIR and HLA genes

Disease	KIR	HLA	Disease progression	Proposed contribution by KIRs	Reference
AIDS	*3DS1*	*HLA-Bw4^{Ile80}*	Decreased	Less inhibition	(2)
	3DS1 homozygous	No *HLA-Bw4^{Ile80}*	Increased	More inhibition	
HCV infection	*2DL3* homozygous	*HLA-C1* homozygous	Decreased	Less inhibition	(4)
Cervical neoplasia (HPV-induced)	*3DS1*	*HLA-C1* homozygous and no *HLA-Bw4*	Increased	Less inhibition	(1)
	No *3DS1*	*HLA-C2* and/or *HLA-Bw4*	Decreased	More inhibition	
Malignant melanoma	*2DL2* and/or *2DL3*	*HLA-C1*	Increased	More inhibition	(8)
Psoriatic arthritis	*2DS1* and/or *2DS2*	*HLA-C1* homozygous or *HLA-C2* homozygous	Increased	Less inhibition	(5)
Type I diabetes	*2DS2*	*HLA-C1* and no *HLA-C2*, no *HLA-Bw4*	Increased	Less inhibition	(3)
Preeclampsia	*2DL1* with fewer *2DS* (mother)	*HLA-C2* (fetus)	Increased	More inhibition	(6)

(6), a potentially fatal condition caused by incomplete remodeling of spiral arteries in maternal decidua and by high blood pressure during pregnancy. Vascular remodeling is required to provide the fetus with an adequate blood supply. Susceptibility is associated with the combination of HLA-C2 on fetal trophoblast cells and KIR2DL1 on maternal cells, and is further increased by the absence of activating *KIR2DS* genes (6). A potential explanation of these findings is that KIR2DL1 confers a strong inhibition, compared with KIR2DL2 or KIR2DL3, which prevents activation of NK cells during interaction with fetal trophoblast cells in the decidua. In this context, activation of NK cells is thought to facilitate implantation through cytokine production.

Potential mechanisms

NK cells are important regulators of immune responses. Their function extends beyond killing of infected or transformed cells. Interactions with dendritic cells, macrophages, and fetal trophoblast cells can regulate NK cell activity by influencing cytokine production, cytotoxicity, and stimulation of T helper-1 responses. Stimulation of NK cells can be beneficial during virus infections, malignant transformation, and pregnancy, but deleterious in the context of autoimmunity or neoplastic transformation. The latter may be provoked by chronic inflammation, which is a known risk factor in developing cancer during persistent infections. HPV establishes latency by preventing NK-mediated lysis of infected cells (16). It would be interesting to test if HPV infection provokes a proinflammatory cytokine response from NK cells in the absence of cytotoxicity, thereby favoring neoplasia. A simple interpretation of the observed genetic correlations might suggest that KIR3DS1 stimulates cytokine production by NK cells, which contributes to inflammation. However, a few key aspects of NK cell biology need to be considered when interpreting such genetic analyses.

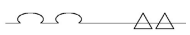
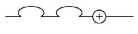
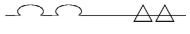
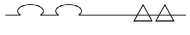
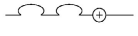
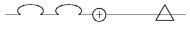
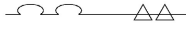
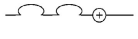
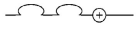
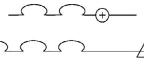
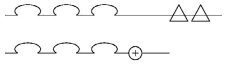
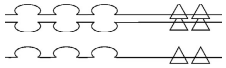
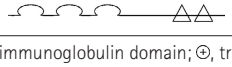
A complex repertoire of polymorphic KIRs

Understanding the basis for the observed genetic associations is complicated by the large repertoire of receptors used by NK cells to interpret their environment. There is extensive polymorphism among KIR haplotypes, which differ not only in nucleotide sequence but also in gene content (17). Different haplotypes carry different numbers of KIR genes, some with few or no activating KIRs (A haplotypes) and others with several activating KIRs (B haplotypes). In addition, each NK cell carries its own repertoire of KIRs. Individuals with several activating KIR genes simply have a higher probability of expressing activating KIRs on any given NK cell than individuals who have fewer activating KIRs. Therefore, a given disease association with HLA–KIR gene combinations, for instance, an activating KIR and its HLA ligand, cannot be interpreted simply as an overall enhancement in NK cell activation signals. Furthermore, a selection process (the mechanism of which is unknown) is in place to ensure that each NK cell has at least one inhibitory receptor specific for a self HLA class I molecule. If, for instance, an NK cell lacks all of the major inhibitory KIRs, it will express the heterodimeric inhibitory receptor CD94–NKG2A (18), which binds to the nonclassical HLA-E. A new inhibitory receptor–ligand combination, which is independent of MHC class I, has recently been discovered on mouse NK cells: binding of NKR-P1 receptors to the widely expressed C-type lectin Clr-b inhibits NK cell activation (19, 20). A similar HLA-independent regulation could also operate in human NK cells. Therefore, it is not clear that KIR haplotypes carrying several activating KIRs would necessarily result in NK cells that are more easily activated, as the expression of activating KIRs should be compensated by the expression of inhibitory receptors.

Elusive role of activating KIR

Activating KIRs are completely dispensable, as KIR haplotypes lacking all functional 2DS and 3DS genes are common (21). In addition, all individuals have a subset of NK cells that are completely devoid of activating KIRs. As activating and inhibitory KIRs are not coordinately expressed, it is unlikely that activating KIRs contribute

Table II. KIR molecules and their HLA ligands

KIR	Structure	Ligand	K_d (reference)	Signaling	Function
2DL1		HLA-C2^{Lys80}	~10 μM (30)	ITIM	Inhibition
2DS1		HLA-C2^{Lys80} (weak)		DAP12	Activation
2DL2[a]		HLA-C1^{Asn80}	~10 μM (31)	ITIM	Inhibition
2DL3[a]		HLA-C1^{Asn80}	~7–9 μM (30, 32)	ITIM	Inhibition
2DS2		HLA-C1^{Asn80} (weak)		DAP12	Activation
2DL4		HLA-G		?	Activation
2DL5		?		ITIM	Inhibition
2DS3		?		DAP12	Activation
2DS4		?		DAP12	Activation
2DS5		?		DAP12	Activation
3DL1[b]		HLA-Bw4		ITIM	Inhibition
3DS1[b]		?		DAP12	Activation
3DL2		HLA-A (weak)		ITIM	Inhibition
3DL3		?		ITIM	Inhibition

⌒, extracellular immunoglobulin domain; ⊕, transmembrane charge; △, cytoplasmic ITIM.
[a]2DL2 and 2DL3 segregate as alleles.
[b]3DL1 and 3DS1 segregate as alleles.

to the function of inhibitory KIRs. The ligand specificity of activating KIRs is unclear. KIR2DS1 and KIR2DS2 may bind HLA-C with a lower affinity than that of closely related inhibitory KIRs (12, 14), but it is also possible that alternate ligands exist, such as the non-HLA ligand for KIR2DS4 on melanoma cells (22). In the mouse Ly49 receptor family, which is structurally distinct from but functionally equivalent to human KIRs, the activating Ly49H and the inhibitory Ly49I receptors bind to the m157 protein of mouse cytomegalovirus (23, 24), suggesting that KIRs may also have viral protein ligands. It is essential to determine the ligand specificity of activating KIRs in order to interpret genetic correlations with diseases. It is also possible that activating KIRs have ligand-independent functions.

Expression of activating KIRs on subsets of T cells could contribute to some of the associations seen in the genetic studies. It is conceivable that activating KIRs may synergize with TCR-mediated signals to cause aberrant immune activation and autoimmune reactions. KIR2DS2, which is expressed by a large percentage of $CD4^+CD28^-$ T cells in rheumatoid arthritis patients with vascular complications, is also a genetic risk factor for this disease (25). Even though T cells lack DAP12, expression of KIR2DS2 costimulated TCR signals which, although suboptimal, resulted in cytokine secretion (26).

Peptide selectivity in recognition of HLA by KIR

Side chains that extend out of the peptide-binding groove of HLA-B and HLA-C molecules can interfere with binding of inhibitory KIRs (10). Although peptide-specific recognition by activating KIRs has been proposed as a potential mechanism to activate NK cells during infections, it is extremely unlikely that self/nonself discrimination is achieved by KIRs, primarily because each KIR binds to different HLA-B or HLA-C molecules, each of which has its own rules for peptide binding. Therefore, recognition by KIR can only work if the peptide does not contribute to specificity. The extensive polymorphism of HLA class I and the very limited repertoire of KIR are not compatible with peptide-specific binding to HLA class I in the context of diseases or infections.

In contrast, CD94 binding to the nonpolymorphic HLA-E is governed by peptide specificity (9). HLA-E normally binds a peptide derived from signal sequences of other HLA class I molecules, and recognition by CD94 is lost when HLA-E instead binds a peptide derived from the signal sequence of heat shock protein 60 (27). This "modified self" situation could induce the killing of cells undergoing a stress response by NK cells that are normally inhibited by HLA-E.

The strength of inhibition hypothesis

Several of the genetic studies have suggested a model whereby inhibition of NK cells by some KIR–HLA combinations is stronger than others. In this model, the inhibition by KIR2DL1–HLA-C2 is strongest, followed by KIR2DL2–HLA-C1, and finally KIR2DL3–HLA-C1 (1, 4–6, 17). Accordingly, weaker inhibitory interactions result in greater NK cell activation and better protection from virus infection, or greater susceptibility to autoimmunity. Similarly, in preeclampsia too strong an inhibition by KIR2DL1–HLA-C2 interactions prevents proper NK cell activation (6), which may be required to stimulate vascularization. The results of Carrington et al. (1) also support such a

connection between strength of KIR-mediated inhibition and disease outcome. However, careful affinity measurements by surface plasmon resonance with each of the purified KIR2DL molecules and their HLA-C ligands have resulted in almost identical values (Table II). On the other hand, binding of KIR2DL–Fc fusion proteins to HLA-C followed a pattern consistent with diminishing strength, in the order KIR2DL1>KIR2DL2>KIR2DL3 (13). Differences in inhibitory strength among KIR2DLs may also be related to signaling in the cytosol, and not to HLA-C binding. An interesting feature of KIR2DLs is a requirement for Zn^{2+} in their inhibitory function (28). Kinetic measurements of KIR2DL binding to HLA-C revealed slower off rates in the presence of Zn^{2+}, particularly in the case of KIR2DL1 (14). Thus, it is possible that differences in sustained engagement of KIR due to Zn^{2+} could translate into differences in strength of inhibition.

Concluding remarks

An analysis of receptor–ligand interactions in the context of diseases is required to understand how HLA–KIR genotypes contribute to disease. It will be important to determine in what tissue and with what ligand-expressing cells are KIR-expressing NK cells and T cells interacting. Such questions are difficult to address, as the lack of KIR conservation in mice precludes the use of a convenient animal model.

Whether the published correlations will hold up to further scrutiny remains to be seen. A major effort is underway to type KIR gene polymorphism and expression in the context of KIR-mismatched bone marrow transplantation (17). The same typing techniques can be applied to refine disease associations. Will a precise analysis of KIR alleles and KIR expression, rather than overall genotypes, result in stronger associations or loss of statistical significance? It is also possible that the strong linkage disequilibrium within the KIR gene complex accounts for disease associations, and that a linked gene is responsible for the observed effect. HLA–disease associations were first reported in the 1970s (29), a decade before the realization that HLA molecules bind peptides, and two decades before the resolution of TCR–MHC structures. Hopefully a molecular basis for the new disease associations with HLA–KIR gene combinations will be provided before the year 2025.

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