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HLAs, TCRs, and KIRs, a Triumvirate of Human Cell-Mediated Immunity

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Abstract

In all human cells, human leukocyte antigen (HLA) class I glycoproteins assemble with a peptide and take it to the cell surface for surveillance by lymphocytes. These include natural killer (NK) cells and γδ T cells of innate immunity and αβ T cells of adaptive immunity. In healthy cells, the presented peptides derive from human proteins, to which lymphocytes are tolerant. In pathogen-infected cells, HLA class I expression is perturbed. Reduced HLA class I expression is detected by KIR and CD94:NKG2A receptors of NK cells. Almost any change in peptide presentation can be detected by αβ $CD8^+$ T cells. In responding to extracellular pathogens, HLA class II glycoproteins, expressed by specialized antigen-presenting cells, present peptides to αβ $CD4^+$ T cells. In comparison to the families of major histocompatibility complex (MHC) class I, MHC class II and αβ T cell receptors, the antigenic specificity of the γδ T cell receptors is incompletely understood.

Contents

INTRODUCTION

The major histocompatibility complex (MHC) was first investigated during the 1930s and 1940s, as a system of variable cell surface antigens that differed among inbred mouse strains and caused skin to be rejected when it was transplanted from one mouse strain to another (1–5). In the 1950s, the homologous system of human leukocyte antigens (HLAs) began to be explored, using serological analysis in which the serum donors were multiparous women who had become sensitized to the paternal HLA expressed by their progeny during pregnancy (6–9). Starting in the 1960s, a continuing series of international collaborations and workshops showed that the HLAs are encoded by a system of closely linked and highly polymorphic genes that is the human homolog of the mouse MHC. Although first studied in the nonphysiological context of allogeneic transplantation, the MHC was subsequently shown to have physiological roles at the center of both the adaptive and innate immune responses to infection.

The highly polymorphic HLA antigens arise from amino acid sequence variation in the closely related families of HLA class I and II membrane glycoproteins. Stable assembly of these glycoproteins and their presence at the cell surface require intracellular binding of a peptide; for MHC class I it is usually a nonamer, but it is less constrained in length when binding to MHC class II. In healthy tissues, the MHC-bound peptides all derive from the degradation of human self-proteins to which T cells are tolerant. By contrast, in the presence of infection, complexes of pathogen-derived peptides and MHC class I or II are recognized by the αβ receptors of T cells to initiate the adaptive immune response. The $CD8^+$ T cells respond to intracellular pathogens, whereas $CD4^+$ T cells respond to extracellular pathogens.

A second lineage of T cells expresses antigen receptors comprised of γ and δ chains that are not strongly biased to the recognition of complexes of peptide and MHC. These γδ T cells contribute to the innate immune response and recognize a variety of different ligands, including phosphoantigens (pAgs), B7-like proteins, and some MHC class I–like proteins (10).

All human MHC class II glycoproteins are dedicated to adaptive immunity and the presentation of peptide antigens to the αβ receptors of $CD4^+$ T cells. Although all highly polymorphic MHC

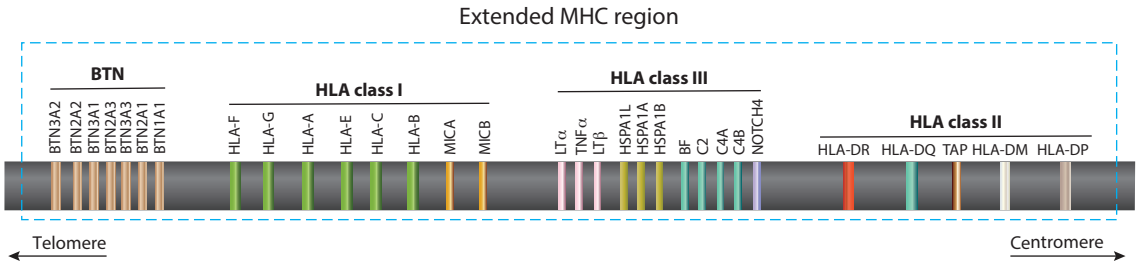

Figure 1

Gene map of the extended MHC region. The extended MHC region is boxed with a dashed blue line. It spans 7.6 Mb from telomere to centromere on the short arm of chromosome 6. Some of the most thoroughly characterized genes are shown, including the butyrophilin (*BTN*), HLA class I, HLA class III, and HLA class II genes.

class I glycoproteins are ligands for the αβ receptors of $CD8^+$ T cells, some are also ligands for the killer cell immunoglobulin-like receptors (KIRs). The KIRs are highly species specific and principally expressed by natural killer (NK) cells. These lymphocytes of innate immunity also contribute to formation of the placenta during reproduction.

THE *HLA* GENE COMPLEX

The *HLA* complex is the most gene-dense region of the human genome. It is present on the short arm of chromosome 6 (6p21.31) and divides into three regions (**Figure 1**). The *HLA* class I region contains three classical genes, *HLA-A*, *HLA-B*, and *HLA-C*, that are expressed by almost all nucleated cells. The *HLA* class II region contains the *HLA-DP*, *HLA-DQ*, and *HLA-DR* genes, which encode proteins that are expressed constitutively by professional antigen-presenting cells, such as dendritic cells, macrophages, and B cells. In an inflammatory environment, other cell types are induced to express HLA class II.

The HLA-A, -B, and -C class I and HLA-DP, -DQ, and -DR class II molecules exhibit an extraordinary diversity (**Table 1**). More than 18,000 class I and 7,000 class II alleles have been defined (**https://www.ebi.ac.uk/ipd/imgt/hla/**). Much of their sequence diversity is located in the antigen-binding sites of HLA class I and II, which provides evidence for strong selection pressures that the various and specific interactions with T cell receptors (TCRs) and KIR impose on these sites.

HLA-E, *HLA-F*, and *HLA-G*, the nonclassical HLA class I genes, have limited polymorphism and a tissue-restricted expression pattern. MHC class I–related chain A and B genes (*MICA* and *MICB*, respectively) are at the centromeric end of the HLA class I region (**Figure 1**). *MICA* is the most polymorphic nonclassical class I gene, with 109 alleles being reported (**https://www.ebi.ac.uk/ipd/imgt/hla/**). All the nonclassical class I genes encode ligands recognized by NK cell receptors (11–14). Within the HLA class II region, *HLA-DO* and *HLA-DM* have little diversity and encode chaperones that facilitate the loading of HLA-DP, -DQ, and -DR with antigenic peptides (15, 16). The HLA class III region is between the class I and II regions and contains genes encoding complement components, heat-shock proteins, and tumor necrosis factor α (TNFα) (**Figure 1**).

HLA Haplotypes and the Extended MHC Region

HLA genes are so closely linked that the *HLA* complex is usually inherited en bloc in classical Mendelian fashion. In this context, the combination of *HLA* alleles that segregate together is called the *HLA* haplotype. At a frequency of ~1% (17), meiotic recombination produces new,

Table 1 Systematic nomenclature established by the WHO Nomenclature Committee for Factors of the HLA System[a]

HLA allotype	Number of HLA allotypes
HLA-A	3,629
HLA-B	4,572
HLA-C	3,447
HLA-E	12
HLA-F	6
HLA-G	19
HLA class I	11,685
HLA-DP	3,160
HLA-DQ	1,278
HLA-DR	1,055
HLA-DM	11
HLA-DO	8
HLA class II	5,512

[a]All HLA protein allotypes, encoded by over 25,000 *HLA* alleles, that were deposited in the IPD-IMGT/HLA database by November 2019 (**https://www.ebi.ac.uk/ipd/imgt/hla/**).

recombinant *HLA* haplotypes. Particular haplotypes, such as the *HLA-A1*, *B8*, *DR3* haplotype in people of European origin, have much higher frequency than expected from random segregation (18). This phenomenon of linkage disequilibrium is in part the consequence of a limited interbreeding between modern and ancient humans, followed by selection for the ancient *HLA* haplotype (19). For modern humans migrating out of Africa, the benefit of the ancient *HLA-A1*, *B8*, *DR3* haplotype could have been one of protection from infectious disease or increased reproductive success. There is also a cost associated with the *HLA-A1*, *B8*, *DR3* haplotype: In European Caucasians today, it is associated with several autoimmune diseases including type 1 diabetes (20), celiac disease (21), and systemic lupus erythematosus (22). The high linkage disequilibrium of *MHC* genes, conserved synteny of *MHC* haplotypes, and presence of other immune system genes outside of the classical *MHC* region led to the concept of an extended *MHC* in humans (23). This extended *MHC* region is 7.6 Mb in length and includes the butyrophilin (*BTN*) genes, one of which encodes BTN3A1, an essential factor for pAg-mediated activation of Vγ9Vδ2 T cells (24) (**Figure 1**).

Architecture of HLA Class I and II

HLA class I comprises a variable α chain, noncovalently associated with invariant β_2-microglobulin (β_2m) (**Figure 2*a***). The homologous α_1 and α_2 domains form the antigen-binding site, consisting of a planar floor of β structure on top of which are two antiparallel α-helices. Between the two helices is the binding site, which accommodates nonamer peptide antigens in extended conformation (**Figure 2*b***). The α_3 and β_2m domains are both immunoglobulin-like domains that interact to form a pedestal that supports the antigen-binding site and projects it away from the cell surface (**Figure 2*a***).

The basic architecture of HLA class II is similar to that of HLA class I. The α_1 and β_1 domains form the antigen-binding site of HLA class II, and α_2 and β_2 are immunoglobulin-like domains that form the supporting structure (25) (**Figure 2*c***). Functionally, the important difference between the structures is that the ends of the peptide-binding site are closed in HLA class I but open in

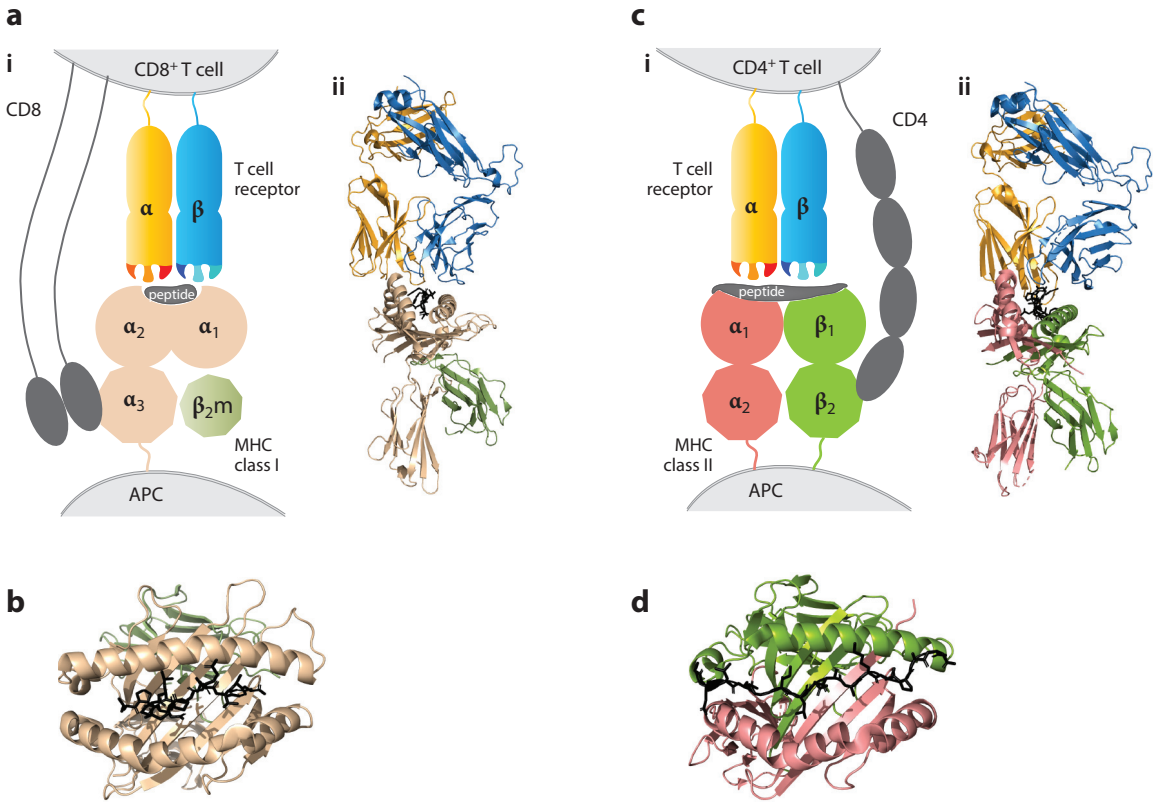

Figure 2

Overview of TCR recognition of peptide–HLA class I and peptide–HLA class II. (*a*, *i*) Schematic depicting interactions between the CDR loops of an αβ TCR of a $CD8^+$ T cell and a peptide–HLA class I complex of an antigen-presenting cell. CD8 binds the conserved α_3 domain of HLA class I. (*a*, *ii*) Crystal structure of an αβ TCR bound to a peptide–HLA class I complex (colored as in *a*, *i*). This structure was obtained from the Protein Data Bank, entry 1OGA (138). (*b*) Overview of peptide (*black stick*) in complex with HLA class I (colored as in *a*). (*c*, *i*) Schematic depicting interactions between the CDR loops of an αβ TCR of a $CD4^+$ T cell and a peptide–HLA class II complex of an antigen-presenting cell. CD4 binds the conserved β_2 domain of HLA class II. (*c*, *ii*) Crystal structure of an αβ TCR binding a peptide–HLA class II complex (colored as in *c*, *i*). This structure was obtained from the Protein Data Bank, entry 4E41 (139). (*d*) Overview of peptide (*black stick*) in complex with HLA class II (colored as in *c*). Abbreviations: APC, antigen-presenting cell; CDR, complementarity-determining region; HLA, human leukocyte antigen; TCR, T cell receptor.

HLA class II. This key feature enables HLA class II to bind peptides of longer length than those bound by HLA class I (**Figure 2*d***).

Basics of Antigen Presentation by HLA

Peptides of 8–10 amino acids, cleaved from endogenously synthesized proteins, are presented to $CD8^+$ T cells by HLA class I (**Figure 2*a*,*b***). In healthy cells, these peptides derive from autologous, self-proteins to which $CD8^+$ T cells are tolerant. However, when cells become virus infected, they synthesize viral proteins and present nonamer peptides derived from them on HLA class I. These complexes of self–MHC class I and viral peptide are recognized by $CD8^+$ T cells, which then kill the virus-infected cell.

Peptide presentation by HLA class I is a tightly regulated process that has been intensively studied for almost 30 years (26). In the cytosol, the proteasome degrades proteins into peptides

that are then translocated to the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP). TAP assembles the peptide-loading complex (PLC) by associating with tapasin, a dimer of HLA class I and β_2m, and the chaperones calreticulin and protein disulfide isomerase ERp57 (27). In the PLC, a peptide is loaded onto the dimer of HLA class I and β_2m, which is then released from the ER and transported through the Golgi apparatus to the cell surface for presentation to $CD8^+$ T cells. Peptides and HLA class I that fail to associate are translocated from the ER back to the cytosol for degradation (26).

HLA class II binds peptides and presents them to $CD4^+$ T cells. The peptides derive from exogenous proteins and have usually been generated by lysosomal proteolysis. They are longer, 11 residues or more, than the nonamers presented by HLA class I (**Figure 2*c,d***). The α- and β-subunits of HLA class II are assembled in the ER, where they associate with the invariant chain Ii, a chaperone. The complex of Ii and HLA class II travels through the Golgi apparatus to a late endosome called the MHC class II compartment (MIIC). In the MIIC, Ii is degraded to give a class II–associated Ii peptide (CLIP) that occupies the HLA class II peptide-binding groove. The release of CLIP and its exchange for a specific antigenic peptide are facilitated by HLA-DM, an invariant and specialized form of HLA class II. Having loaded an antigenic peptide, HLA class II is then transported to the plasma membrane, where it presents the antigen to $CD4^+$ T cells (15). In B cells and thymic epithelial cells, the activity of HLA-DM is regulated by HLA-DO, another invariant form of HLA class II, which modulates peptide binding to HLA class II (16).

Both HLA class I and II bind peptides derived from self-proteins and nonself-proteins. Though HLA class I presents endogenously synthesized antigens in most cells, in dendritic cells it can, under some circumstances (28), also present exogenous antigens, which are internalized by endocytosis or phagocytosis and then presented on HLA class I molecules to $CD8^+$ T cells. This phenomenon is called cross presentation. Likewise, endogenous proteins that are degraded through autophagy, or other pathways, can be presented to $CD4^+$ T cells by HLA class II molecules (29).

TCR STRUCTURE AND DIVERSITY

The extracellular domains of the αβ and γδ TCRs recognize antigens and are noncovalently associated with the CD3 signaling complex (30–34) (**Figure 3*a***). The TCR–CD3 complex consists therefore of αβ or γδ TCR chains, which bind antigen, and CD3εδ, CD3γε, and CD3ζζ chain dimers, which transduce signals to the nucleus (**Figure 3*a***). Phosphorylation of ITAMs (immunoreceptor tyrosine-based activation motifs) in the CD3 polypeptides by Src-family kinases initiates downstream signaling from the TCR (35).

TCRs recognize a broad diversity of antigens with a high degree of specificity. This is achieved by a strategy of somatic combinatorial gene assembly (36). The exons that encode the variable regions of TCRs are assembled in developing T lymphocytes from variable (V), diversity (D), and joining (J) gene segments, using site-specific recombination. The TCR β and δ chain exons are assembled from V, D, and J segments, whereas the TCR α and γ chain exons are assembled from V and J segments (**Figure 3*b***). Each *TCR* locus consists of these gene segments plus one or more exons encoding a TCR constant region (36, 37).

The human δ chain gene is situated within the α chain gene on chromosome 14, between the Vα and Jα gene segments. In contrast, the β and γ chain genes are apart at different sites on chromosome 7 (37, 38). The α and β chain genes have many more V and J gene segments than the γ and δ chain genes (**Figure 3*b***). Only six Vγ genes function, and Vδ1, Vδ2, and Vδ3 are the only Vδ segments. Five Vα segments are interspersed with Vδ segments, but they are rarely used in δ chain rearrangements (39). Restriction of some V segments to particular tissues further decreases

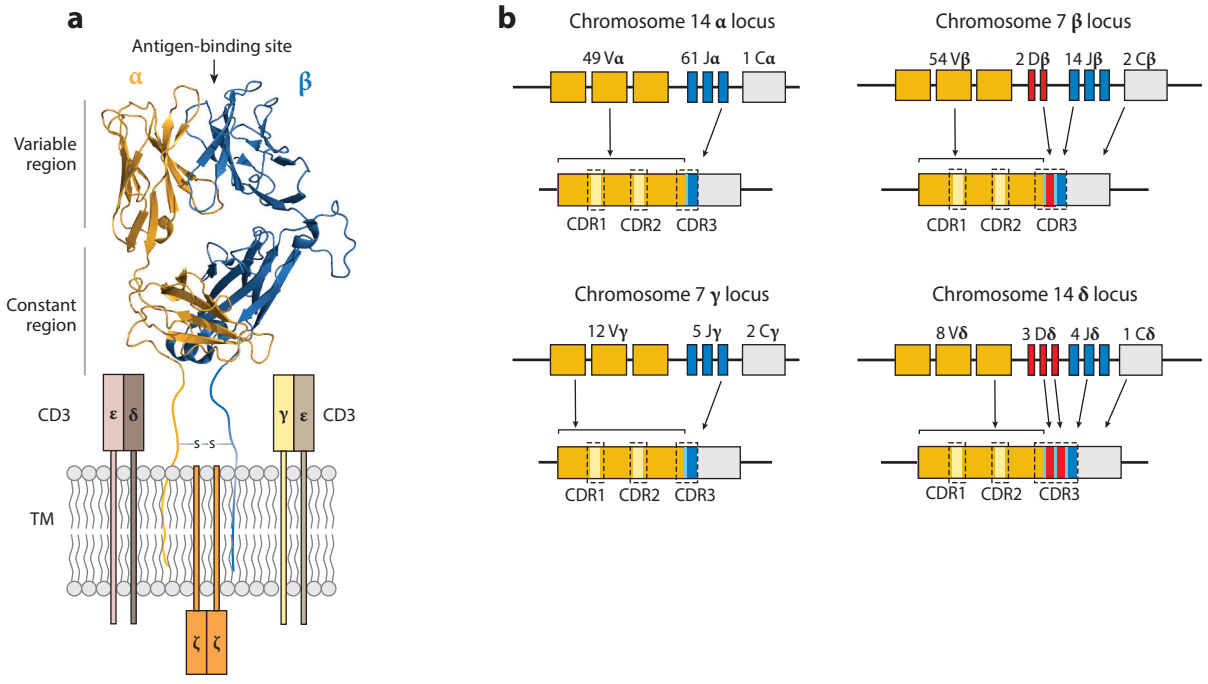

Figure 3

Overview of the TCR–CD3 complex and the genetic recombination of TCR genes. (*a*) Ectodomains of the αβ heterodimer associate with the CD3 εδ, CD3 γε, and CD3 ζζ dimers embedded in the plasma membrane. The crystal structure of the αβ heterodimer was obtained from the Protein Data Bank entry 1OGA (138). (*b*) Genetic recombination of TCR genes from the α, β, γ, and δ loci. Variable (V), joining (J), diversity (D), and constant (C) gene segments are depicted in yellow, blue, red, and gray, respectively. Segments from each region are recombined, with nucleotide additions in the junctions between V, D, and J gene segments (depicted in *cyan*), to generate each rearranged TCR. CDR1, CDR2, and CDR3 are outlined by dashed boxes. CDR1 and CDR2 are encoded by the V region, whereas CDR3 straddles the V(D)J junction. Abbreviations: CDR, complementarity-determining region; TCR, T cell receptor; TM, transmembrane.

γδ TCR diversity. However, TCR δ exons can incorporate multiple D segments (**Figure 3*b***), which increases the junctional diversity and gives the δ chain a higher potential diversity than the other TCR chains (40).

A diverse TCR repertoire is thus achieved through combinatorial and junctional diversity. The latter dramatically expands the TCR repertoire by the inclusion of nontemplated nucleotide (N) additions at the V(D)J junctions. The random pairing of TCR chains allows further combinatorial diversity. After immature T cells in the thymus have been subject to negative selection to eliminate strongly self-reactive cells, and positive selection to preserve weakly self-reactive cells, an individual has approximately 2×10^7 αβ TCRs, each expressed by a different clone of T cells (41). Diversity in each TCR chain is confined to three complementarity-determining regions (CDRs) (**Figure 3*b***), each forming a short hypervariable loop. Pairing of TCR chains brings together the six hypervariable loops, creating a single hypervariable surface that forms the antigen-binding site at the membrane-distal end of the TCR extracellular domain. This is the site that engages the complex of peptide antigen and MHC class I or II. CDR1 and CDR2 are germ line encoded by V gene segments. CDR3 is generated by random deletions and the addition of templated and nontemplated nucleotides at the joints between gene segments. It has therefore greater diversity than CDR1 and CDR2 (42).

Conventional T Cells

The αβ T lymphocytes that recognize peptide antigens presented by MHC class I and II are the most abundant T cells and the main effectors of cell-mediated adaptive immunity. For this reason, they are also called conventional T cells. The extensive diversity of αβ TCRs and of polymorphic MHC class I and II enables human immune systems to recognize antigens from almost any pathogen.

CD8 and CD4 are antigen coreceptors that interact with HLA class I and class II, respectively (43–45) (**Figure 2*a*,*b***). In the synapse where target cell HLA class I presents antigen to the αβ TCR of a $CD8^+$ T cell, the CD8 interacts with the conserved immunoglobulin domains of HLA class I (44). Likewise, when HLA class II presents antigen to the αβ TCR of a $CD4^+$ T cell, the CD4 interacts with the conserved immunoglobulin domains of HLA class II (45). Following antigen recognition, the interaction of the TCR with either CD4 or CD8 has a crucial role in generating optimal signals from the additional protein kinase LcK that is recruited through this event (46). This mechanism promotes effective signaling even to small amounts of an antigen.

Unconventional T Cells

Small subpopulations of αβ T cells comprise rare T cells that do not recognize peptide–MHC complexes. Described as unconventional T cells, they have limited TCR diversity. Mucosal-associated invariant T (MAIT) cells, invariant natural killer T (iNKT) cells and germ line–encoded mycolyl reactive (GEM) T cells are all populations of unconventional T cells. MAIT cells have a characteristic TCRα chain comprising Vα7.2 and Jα33 segments. MAIT cells recognize the invariant MHC-related molecule 1 (MR1) and contribute to antibacterial immunity (47, 48). iNKT cells have a TCRα chain containing Vα24-Jα18, and GEM T cells express a TCRα chain containing Vα7.2-Jα9. iNKT cells recognize glycolipids presented by CD1d, whereas GEM T cells recognize glycolipids presented by CD1b (49, 50).

Because γδ T cells do not respond to peptides presented by MHC class I or II, they too are generally considered to be unconventional T cells of innate immunity. Typically, γδ T cells comprise only 0.5–5% of T cells circulating in the blood, lymph, and secondary lymphoid tissues. They are present in greater numbers in some epithelial tissues, a compartmentalization that is particularly pronounced in mice (51). In humans, the major circulating γδ T cells have the Vγ9Vδ2 TCR (alternatively termed Vγ2Vδ2 TCR). Various bacterial and protozoan infections are associated with a massive expansion of Vγ9Vδ2 T cells, in which they represent up to 50% of the circulating T cells (52). These Vγ9Vδ2 T cells respond to pyrophosphate-containing compounds, known in this context as pAgs. They include isopentenyl pyrophosphate (IPP) and (*E*)-4-hydroxy-3-methylbut-2-enyl pyrophosphate (HMBPP) (53, 54). The mechanism by which pAgs activate Vγ9Vδ2 T cells is not well understood, but BTN3A1 clearly plays a part (24), either as an intracellular sensor (55) or in presenting pAgs (56) (**Figure 4**). Yang et al. (57) recently defined the molecular mechanisms underlying the inside-out signaling that supports the intracellular sensing of pAgs by BTN3A1. For decades, Vγ9Vδ2 TCRs were only observed in higher primates, but sequences homologous to human Vγ9 and Vδ2 genes were recently described for alpaca (*Vicugna pacos*), a New World camelid (58).

As well as antibacterial immunity, Vγ9Vδ2 T cells exert antiviral and antitumor activities in vitro, and in humanized mice (59–62). Epstein–Barr virus (EBV)-infected B cell lines that maintain type I latency activate Vγ9Vδ2 T cells to proliferate and produce a large population of effector cells (62). Characteristic of type I EBV infection is the expression of nuclear antigen 1 (EBNA1) and no other viral protein. EBNA1 is present in homeostatically proliferating EBV-infected memory B cells and in Burkitt lymphoma (63), the most common childhood tumor in

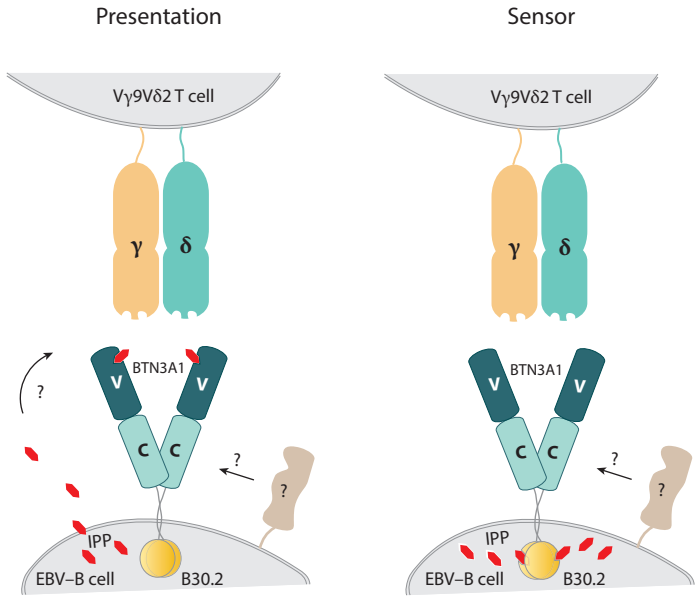

Figure 4

Speculative models for the participation of BTN3A1 in presenting pAgs to Vγ9Vδ2 T cells, applied to type I EBV-infected B cells. (*Left*) In model 1, BTN3A1 directly presents pAgs to the Vγ9Vδ2 TCR using its extracellular domain. It is not known how endogenously generated pAgs (e.g., IPP accumulating in type I EBV-infected B cells) are presented by BTN3A1. Intracellular pAgs could be secreted and then bound directly by BTN3A1 on the same cell or a neighboring cell. The role of the intracellular B30.2 domain in this setting has not been determined. It is likely, however, that BTN3A1 associates with a second protein that enhances pAg presentation. (*Right*) In model 2, BTN3A1 functions as a sensor for intracellular pAgs. BTN3A1 B30.2 domains bind pAgs, leading to conformational changes in BTN3A1. These changes are recognized by Vγ9Vδ2 TCRs. In this model, BTN3A1 could associate with a second protein that optimizes binding of pAgs. Abbreviations: EBV, Epstein–Barr virus; IPP, isopentenyl pyrophosphate; pAgs, phosphoantigens.

sub-Saharan Africa. The infected B cells maintain a high concentration of endogenous IPP, explaining their capacity to activate Vγ9Vδ2 T cells. This activation requires BTN3A1 (**Figure 4**) and, to a lesser extent, NKG2D. Remarkably, 50% of healthy humans make a strong Vγ9Vδ2 T cell response to EBV, whereas the other 50% make a feeble response. This difference has no correlation with gender, HLA type, or prior exposure to EBV or cytomegalovirus. Such bimodal variation in the Vγ9Vδ2 T cell response to EBV is also observed in vivo, among EBV-positive healthy children and children suffering from infectious mononucleosis (62). The even frequencies of Vγ9Vδ2 T cell responders and nonresponders imply there is an advantage to having both responses in human populations. The mechanism of this functional dimorphism remains unknown. However, recent study and comparison of the γδ TCR repertoires of healthy individuals show that those who make a strong response have TCRγ chains enriched for CDR3s containing JγP, whereas a feeble response is correlated with TCRγ chains enriched for CDR3s containing Jγ2 (Z. Djaoud & P. Parham unpublished manuscript). One possible cause of the difference is that these individuals differ in the history of their exposure to microbial pAgs and EBV. Polymorphisms in γ, δ, and other genes affecting γδ T cell development and function are other possible contributors.

Vδ2$^-$ T cells, which are mainly Vδ1$^+$ T cells, are less abundant in peripheral blood, but they are substantially enriched in tissues, particularly epithelia. Unlike Vδ2$^+$ TCR chains, Vδ2$^-$ TCR

chains do not preferentially pair with a specific Vγ chain. Antigens recognized by Vδ2$^-$ TCRs are largely unknown, but Vδ1$^+$ TCRs are known to recognize CD1d, an MHC class I–like molecule, with or without an associated lipid antigen (64). Vδ2$^-$ T cells are associated with the immune response to cytomegalovirus infection, among transplant patients, pregnant women, neonates, and immunodeficient children as well as healthy people (65).

Because the gene segments of the TCRα and TCRδ chains are in the same locus and overlap, they sometimes give rise to a chimeric TCR chain that comprises a TCRδ variable gene (Vδ1) fused to joining α and constant α domains, paired with an array of TCRβ chains. This fully functional δ/αβ TCR, which is used by nearly 50% of human Vδ1$^+$ T cells, recognizes peptide and lipid antigens bound by HLA class I and CD1d, respectively (66). Other interlocus V(D)J rearrangements have been reported (67). Increasing frequency of these chimeric receptors correlates with lymphoma development (67).

T Cells in the Thymus

The diversity of the T cell repertoire principally arises in immature thymocytes through V(D)J recombination. This repertoire is then subject to coordinated processes of selections that occur during T cell development. They include positive selection and negative selection, each of these being determined by the interactions of the TCRs with self-MHC ligands in the thymus. T cell precursors expressing a TCR differentiate in the cortex of the thymus into thymocytes expressing both CD4 and CD8. Low-affinity interactions of a thymocyte's TCR with complexes of MHC on thymic epithelial cells in the cortex lead to positive selection and commitment of the cell to either the CD4 or the CD8 lineage, depending on whether the selection was mediated by MHC class I or class II. Thymocytes that receive insufficient signaling are induced to undergo apoptosis (68). In contrast, the selected thymocytes migrate to the medulla, where they interact with medullary thymic epithelial cells and dendritic cells that present a larger set of complexes of MHC class I and II with self-peptides. All CD4$^+$ and CD8$^+$ thymocytes that recognize with high affinity a complex of self-peptide with MHC class I or II are induced to die by apoptosis. This clonal deletion is called negative selection. By the mechanisms of positive and negative selection, the individual develops a T cell repertoire that is tolerant of human self-proteins and well equipped to respond to the proteins of pathogens (69).

Compared to αβ T cells, little is known of γδ T cell selection. The αβ and γδ T cells derive from a common progenitor in the thymus (70). Commitment to the γδ T cell lineage appears to be controlled by the γδ TCR. Two studies showed that quantitative differences in TCR signal strength could mediate commitment of a single γδ TCR to either the αβ or the γδ lineage pathway. Strong signals favor the γδ T cell lineage, whereas weak signals favor the αβ T cell lineage (71, 72). This model suggests that γδ TCRs need to interact with their ligands in the thymus. However, since ligands for γδ T cells are not well defined, the process of a potential positive selection for γδ T cells in the thymus continues to be a matter of debate.

OVERVIEW OF THE KIR

As for CD8$^+$ T cells, receptors for HLA class I are central to the biology of NK cells, lymphocytes of innate immunity and reproduction. However, in contrast to αβ TCRs that bind antigenic peptides bound to HLA class I, receptors expressed on NK cells detect downregulation of HLA class I on unhealthy cells. Thus, in most circumstances, these receptors prevent NK cells from responding to healthy cells expressing normal levels of HLA class I molecules. To diversify their receptors for HLA, NK cells do not use gene rearrangement and somatic mutation. Instead, they use transcriptional regulation of a number of receptor genes to form a diverse repertoire with heterogeneous NK cell subpopulations.

Two main categories of inhibitory receptors for HLA class I have been defined in humans, the conserved CD94/NKG2A heterodimer (11, 73, 74), belonging to the C-type lectin-like superfamily, and the highly diverse KIR family (75, 76). Mouse NK cells also have a CD94:NKG2A receptor with functions similar to those of its human counterpart. However, mice do not have KIR; instead, they express Ly49, a different family of diverse receptors with specificity for MHC class I ligands. KIR and Ly49 receptors are phylogenetically and structurally unrelated (77), although they both recognize diverse MHC class I ligands. The one human Ly49 gene is not functional (78).

Interactions between HLA class I ligands and cognate NK cell receptors during NK cell development enable mature NK cells to monitor other cells for the quality and quantity of their HLA class I expression. Moreover, the strength of these interactions determines the strength of NK cell responses to infection and malignancy. This learning process is known as NK cell education (79, 80). The inhibitory CD94:NKG2A recognizes HLA-E, the oldest HLA class I isotype (11). Both CD94:NKG2A and HLA-E are conserved within human populations. Thus, all individuals have NK cells educated by CD94:NKG2A. On the other hand, the ligands for inhibitory KIR are four epitopes of HLA-A, -B, and -C. The extent to which a person's NK cells are educated by KIR is variable and depends on an individual's KIR and HLA class I type (79, 81, 82). NK cell education is thus achieved by two complementary systems of HLA class I ligands and inhibitory receptors: the ancestral and conserved school using CD94:NKG2A with HLA-E, and the younger and highly diverse school using the combinations of KIR with HLA-A, -B, and -C (82) (**Figure 5**).

Physiologically, the peptides that are loaded into the HLA-E groove are predominantly nonamers derived from the leader sequences of HLA-A, -B, and -C. These nonamers correspond to residues −22 to −14 of the HLA class I heavy chain and have methionine at position −21 (−21M). On loading the right peptide, HLA-E translocates to the cell membrane, where it is recognized by the CD94:NKG2A receptor of NK cells (11). Although all HLA-A and HLA-C allotypes have −21M, most HLA-B allotypes have threonine at position −21 (−21T), with a minority having −21M. The −21M/T dimorphism of HLA-B, the most highly expressed HLA class I, has significant influence on the cell surface expression of HLA-E. Consequently, in comparison to homozygous −21T individuals, the homozygous and heterozygous −21M HLA-B individuals have higher expression of HLA-E, which increases the education of CD94:NKG2A$^+$ NK cells (82) (**Figure 5**).

Genetic analysis of human populations worldwide shows that HLA haplotypes with −21M HLA-B rarely encode KIR ligands with Bw4 and C2 motifs. Furthermore, the 3′ untranslated region of HLA-C binds a microRNA (miR-148a) that affects HLA-C expression (83). A polymorphism in this region that prevents microRNA binding is in complete linkage disequilibrium with the HLA-B polymorphism at position −21. Consequently, the C1$^+$ HLA-C allotypes encoded by −21M HLA-B haplotypes are expressed at lower levels. These features divide HLA haplotypes into two distinctive groups: one preferentially providing ligands that educate CD94:NKG2A$^+$ NK cells, and the other providing ligands that educate KIR$^+$ NK cells (82) (**Figure 5**).

KIR Expression and KIR Ligands

KIRs are primarily expressed by NK cells but also by subpopulations of αβ and γδ T cells (84–86). KIR2DL4 is unique in being expressed by all NK cells. The other KIRs are clonally expressed in stochastic fashion to generate a repertoire of NK cells expressing different combinations of KIRs (87, 88). It is proposed, but not proven, that this clonal diversity makes the NK cell population more sensitive to the loss of HLA class I expression that occurs in virus-infected or transformed cells.

The known ligands of inhibitory KIRs are four epitopes of HLA-A, -B, and -C (**Figure 6**). The A3/11 epitope of HLA-A*03 and HLA-A*11 is recognized by KIR3DL2 (89, 90). KIR3DL1

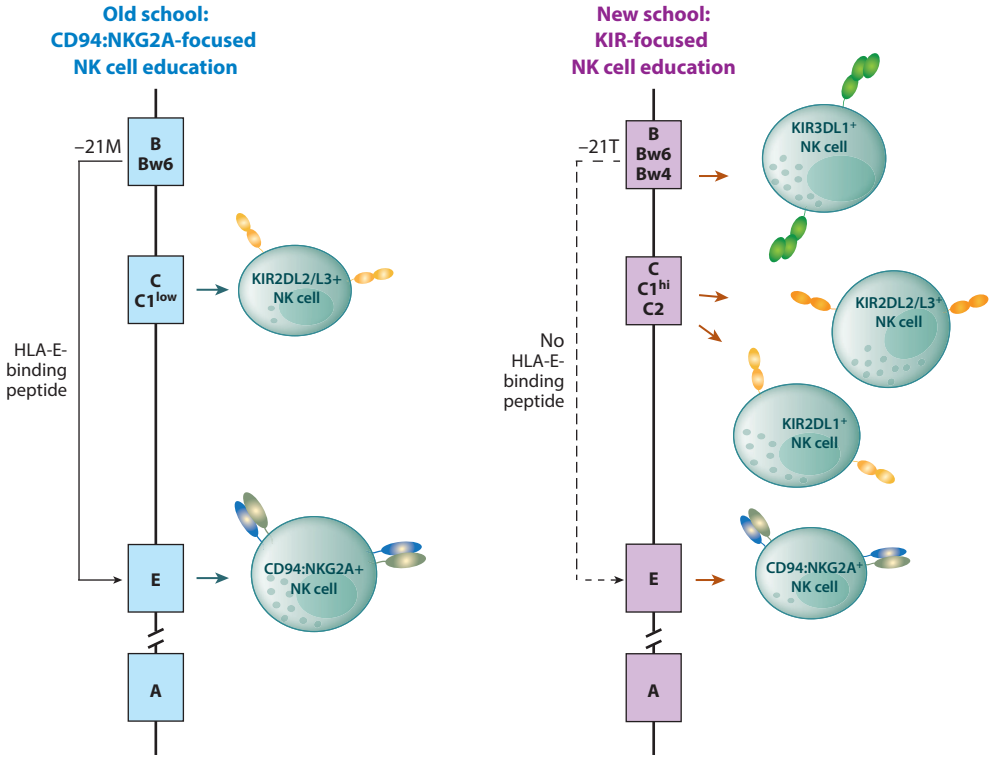

Figure 5

Class I HLA haplotypes define two complementary schools for NK cell education. (*Left*) Ancestral haplotypes with −21M HLA-B and -C1 educate NK cells through interactions between conserved CD94:NKG2A and HLA-E. (*Right*) In contrast, younger haplotypes with −21T HLA-B provide various combinations of Bw4, C1, and C2 ligands and educate NK cells through diverse polymorphic KIR. Abbreviation: NK, natural killer.

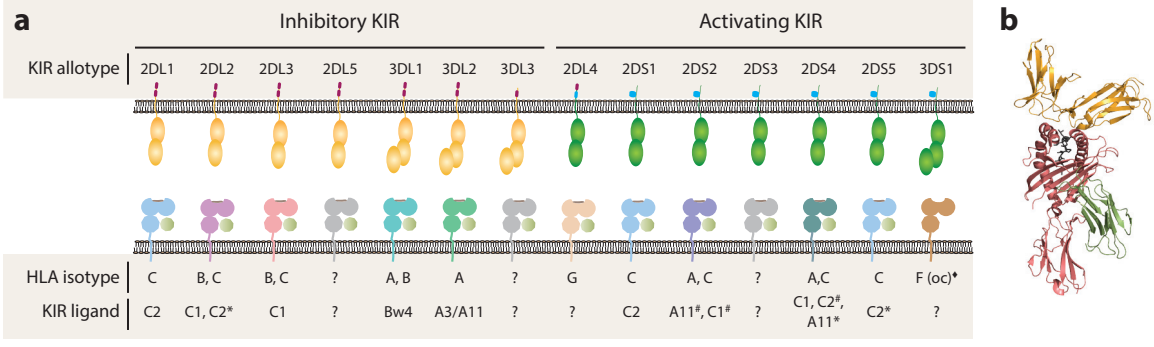

Figure 6

KIRs and their HLA class I ligands. (*a*) KIRs have either inhibitory (*yellow*) or activating (*green*) functions. The known HLA isotypes and epitopes recognized by KIRs are given. A question mark indicates KIR ligands that are not yet defined. An asterisk indicates that only the subset of HLA variants with the listed epitope bind (101, 140, 141). A number sign indicates interactions that require an appropriate peptide (110–113). A diamond indicates that HLA-F open conformers with no bound peptide are also ligands of lower affinity for KIR3DL1 and KIR3DL2 (12). (*b*) Crystal structure of KIR2DL2 bound to complex with HLA-C*03:04 (colored as in panel *a*). The crystal structure was generated from the Protein Data Bank, entry 1EFX (142). Abbreviation: oc, open conformers.

recognizes the Bw4 epitope carried by subsets of HLA-A and -B allotypes and defined by a sequence motif at positions 77–83 in the α_1 domain (91, 92). KIR3DL1 has an extensive functional polymorphism, which affects its cell surface expression (80, 93) and interactions with Bw4 (94, 95). Polymorphism within and outside of the Bw4 motif affects its avidity for KIR3DL1, as do changes in the sequence of the bound peptide (96–98).

Dimorphism at position 80 in the α_1 domain of HLA-C determines the C1 and C2 epitopes recognized by lineage III KIRs. The C1 epitope is defined by asparagine 80, and the C2 epitope is defined by lysine 80 (99). The specificity of the lineage III KIRs that recognize the C1 and C2 epitopes is determined by dimorphism at position 44 in the D1 domain. KIR2DL1 has lysine 44 and specificity for C2, whereas KIR2DL3 has asparagine 44 and specificity for C1 (100). In addition to dimorphism at position 80, HLA-C has other variable positions that modulate the affinity and specificity for KIRs (101–103). Likewise KIR2DL1 and KIR2DL3 have many variable positions other than 44 that modulate their affinity and specificity for HLA-C (104–107).

The considerable sequence homology between the extracellular domains of the activating and inhibitory KIRs suggests that activating KIRs also recognize HLA class I (**Figure 6**). However, their specific ligands are less clearly defined, which is probably due to their low affinity for HLA class I and their high peptide selectivity. Natural variants of KIR2DS1, for instance, recognize HLA-C2 with a range of avidity (108, 109). KIR2DS2 recognizes HLA-A11 and HLA-C1 in a peptide-specific fashion (103, 110, 111). A recent study shows that NK cells expressing KIR2DS2 are activated by a conserved peptide of flaviviruses that is bound by HLA-C*01:02 (112). In similar fashion, Sim et al. (113) discovered that KIR2DS4 recognizes the complex of a conserved bacterial peptide and HLA-C*05:01. This recognition is sufficient to activate NK cells, pointing to a contribution of NK cells to antibacterial immune defense (113). Lastly, a study has shown that the open conformers of HLA-F present on activated T cells are high-affinity ligands for KIR3DS1 (12). These findings suggest that, like αβ TCRs, activating KIRs can recognize altered self–HLA class I molecules in the context of infection or cancer.

KIR Gene Diversity

The human *KIR* locus is characterized by gene content variability and allelic polymorphism (114). This locus on chromosome 19q13.4 comprises a family of 16 genes and pseudogenes that occupy ~150 kb of the leukocyte receptor complex (**Figure 7**). It is flanked on the centromeric side by the *LILR* genes and on the telomeric side by the *FCAR* and *NCR1* genes, which respectively encode the Fc receptor for monomeric IgA and the natural cytotoxicity receptor 1 of NK cells. Four *KIR* genes, *KIR3DL3*, *KIR3DP1*, *KIR2DL4*, and *KIR3DL2*, are present in all individuals and comprise the framework genes of the locus. *KIR3DL3* and *KIR3DL2* genes mark the centromeric and telomeric ends of the locus, respectively, while *KIR2DL4* and the *KIR3DP1* pseudogene mark the central part of the locus (115, 116). This divides the *KIR* locus into centromeric and telomeric regions, which vary in both the number and kind of *KIR* genes they contain (117) (**Figure 7**).

KIR genes form two haplotype groups, *A* and *B* (**Figure 7**). *KIR A* haplotypes combine one activating *KIR* gene, *KIR2DS4*, with several inhibitory *KIR* genes (*KIR2DL1*, *KIR2DL3*, *KIR3DL1*, and *KIR3DL2*). These genes are common to *KIR A* and *B* haplotypes. However, *KIR B* haplotypes are characterized by the presence of one or more of six *B*-specific KIR genes: *KIR2DL5*, *KIR2DS1*, *KIR2DS2*, *KIR2DS3*, *KIR2DS5*, and *KIR3DS1*. Consequently, *KIR B* haplotypes have increased *KIR* gene content and number of activating *KIR* genes compared to *KIR A* haplotypes (117). Furthermore, a null allele of the *KIR2DS4* gene is prevalent in human populations (118). Thus, many individuals who are homozygous for *KIR A* haplotypes have no activating KIR. Typically, individuals have 14 to 24 *KIR* genes (7 and 12 *KIR* genes per haplotype). *A* and *B* haplotypes

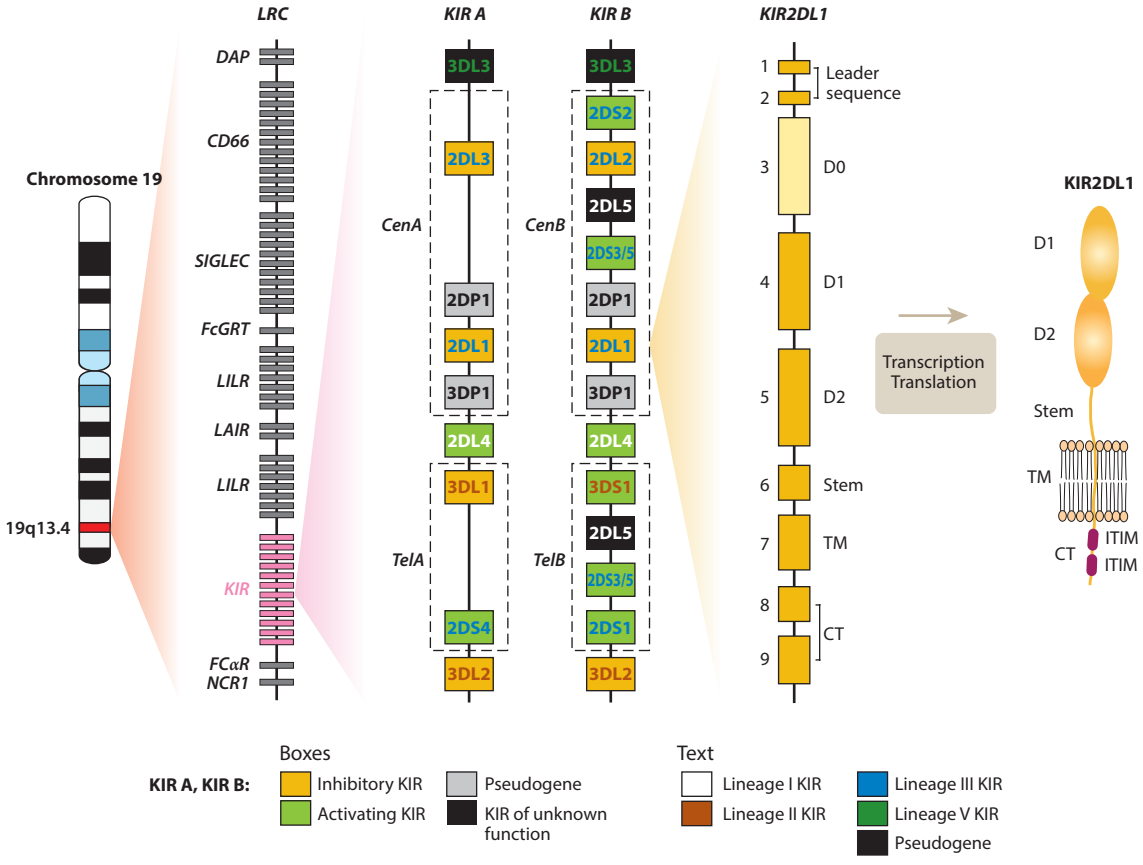

Figure 7

Overview of the *KIR* gene and protein structures. *KIR* genes are located on chromosome 19, within the LRC. They are organized into *A* and *B* haplotypes. The shortest *KIR A* and the longest *KIR B* haplotypes are given. *CenA*, *CenB* and *TelA*, *TelB* are centromeric and telomeric regions of the *A* and *B* haplotypes, respectively. Exons of the *KIR2DL1* gene and its encoded KIR2DL1 protein are given. Exon 3 (*light yellow*) is a pseudoexon for KIR2DL1. KIR nomenclature is based on their protein structure: 2D and 3D denote 2 or 3 immunoglobulin domains; L and S are for long and short cytoplasmic tails, respectively; and P is for pseudogene (143). The phylogenetic lineages of KIRs are given: KIR2DL4 and KIR2DL5, lineage I; KIR3D specific for HLA-A and HLA-B, lineage II; KIR specific for HLA-C, lineage III; KIR3DL3, lineage V. D0, D1, and D2 are immunoglobulin domains. Abbreviations: CT, cytoplasmic tail; ITIM, immunoreceptor tyrosine-based inhibitory motif; LRC, leukocyte receptor complex; TM, transmembrane.

are both represented in all human populations, but their frequencies vary widely between ethnic groups (119). An additional dimension to KIR diversity is allelic polymorphism, a property of most *KIR* genes. Like *HLA* class I genes, some *KIR* genes are highly polymorphic, whereas others are conserved or have low polymorphism. Because KIRs functionally interact with HLA class I, the variability in their combination is compounded (120). The Immuno Polymorphism Database (IPD)-KIR database currently defines 977 *KIR* alleles (**https://www.ebi.ac.uk/ipd/kir/**).

Coevolution of KIRs and MHC Class I

The diversified KIR and MHC class I system of interacting NK cell receptors and ligands is specific to the simian primates and cattle (121). Comparison of the KIR and MHC loci between

different primate species shows, however, an exceptional degree of species specificity that attests to the rapid coevolution of this system. For instance, the emergence of the MHC-C locus that supplies ligands for lineage III KIRs is unique to hominids. Furthermore, the balance between the two groups of *KIR* haplotypes that is present in all human populations is unique to humans. Strong competing pressures from immunity and reproduction place these two haplotypes under balancing selection: *A* haplotypes, enriched for genes that encode KIRs with high affinity for HLA class I, favor successful immune defense, whereas *B* haplotypes, enriched for genes that encode KIRs with low affinity for HLA class I, favor successful reproduction (122).

Study of indigenous and anthropologically well-characterized human populations shows how KIRs and HLA class I correlate in frequency across the world (123). This phenomenon is well illustrated by the Yucpa Amerindians, who have an unusually high frequency of HLA-C7 and evolved two unique KIR2DL3 variants with reduced binding to C1 (106). In analogous fashion, the KhoeSan of southern Africa, who have an unusually high frequency of HLA-C allotypes having the C2 epitope, evolved two unique KIR2DL1 variants. One of them switched its binding specificity from C2 to C1, and the other one has no functional interactions with C2 (105). In another scenario, the Māori of New Zealand have a low frequency of $Bw4^+$ HLA-B, combined with an increased frequency of HLA-A allotypes recognized by lineage II KIRs (124). In all these populations, coevolution of KIRs and HLA class I maintains a balanced NK cell function despite changes in the frequency of KIR ligands supplied by HLA class I.

KIRs and HLA Class I in Disease

The extraordinary polymorphism of *HLA* class I and *KIR* and their segregation on two different chromosomes led to extensive genetic studies that correlated disease incidence with the combined expression of these two families of genes or the expression of each of them separately. Hundreds of *KIR* gene associations with disease resistance or susceptibility have been published. Effects have been reported in infectious disease, autoimmune or idiopathic disease, pregnancy disorder, cancer, chronic inflammatory disease, and the outcome of hematopoietic stem cell transplantation. A recently developed database, named KIR and Disease Database (KDDB), compiling these genetic association studies is now available within the Allele Frequency Net Database (AFND) (125).

KIRs in Pregnancy Disorders

During pregnancy, interactions of the fetal trophoblast with maternal NK cells help extravillous trophoblast (EVT) cells to elaborate large vessels from the mother's spiral arteries, ensuring that the growing fetus will receive a sufficient blood supply until term. These NK cells, which have unique phenotype and function, are the dominant leukocytes in the uterine tissue during the first trimester and then begin to diminish in number midway through gestation (126). The extent of the arterial transformation in the uterus directly affects the success of gestation. Indeed, insufficient placental blood supply can lead to preeclampsia, stillbirth, or fetal growth restriction. In contrast, an extensive placental vascularization results in oversized babies that cannot pass through the birth canal, which is potentially fatal for both mother and child (127). Thus, NK cells are essential for the control of this process through cooperative interactions with trophoblast cells.

EVT cells express HLA-C, -E, and -G but not HLA-A and -B (128). HLA-C provides ligands for KIR2D receptors. HLA-E is a ligand for CD94:NKG2A and CD94:NKG2C (129). HLA-G, which is expressed only on EVT cells, is a high-affinity ligand for the LILR family (13) and a ligand for KIR2DL4 (130). Of these different interacting systems, only KIR2D/HLA-C is highly polymorphic and can contribute to variation in human pregnancy. Moreover, subpopulations of uterine

NK cells express high levels of KIR2D, including KIR2DL1, KIR2DL2, KIR2DL3, KIR2DS1, and KIR2DS4 (131), for which the genetic variation could directly impact NK cell function. Indeed, mothers homozygous for *KIR A* haplotypes who lack $C2^+$ HLA-C and carry a fetus that inherited paternal $C2^+$ HLA-C are at highest risk for miscarriage, preeclampsia, and fetal growth restriction (132, 133). This is likely due to an excessive inhibition of uterine NK cells, leading to understimulation of the trophoblast and poor placentation. The likely cause of this effect is KIR2DL1, because it has the strongest inhibitory interaction with C2. In line with this interpretation, the presence of a *KIR B* haplotype reduces the risk for preeclampsia in women carrying HLA-C2-expressing fetuses (134–136). Thus, the activating signals mediated by activating KIRs neutralize the inhibitory signal mediated by the KIR2DL1/HLA-C2 interaction. On the other hand, a large cohort study of Norwegian pregnancies has correlated large babies with the presence of *KIR2DS1* in mothers carrying a C2-expressing fetus (137). In this model, KIR2DS1-mediated activation of NK cells might promote an excessive placental invasion by EVT cells.

SUMMARY

The human immune system has evolved several protein families that protect the host from pathogens and promote reproductive success. HLA class I and II, TCRs, and KIRs are central to cell-mediated immunity. *HLA* is the most polymorphic human gene complex. The HLA class I and II glycoproteins present antigenic peptides to αβ T cells and are crucial to cell adaptive immune responses. Through complex pathways of antigen degradation and peptide binding, HLA class I presents peptides from intracellular pathogens to $CD8^+$ T cells, whereas HLA class II presents peptides from extracellular pathogens to $CD4^+$ T cells.

HLA-restricted recognition of antigenic peptides by αβ T cells is mediated by somatically rearranged αβ TCRs, which are expressed by the majority of circulating T cells. A highly diverse αβ TCR repertoire is achieved by combinatorial and junctional diversity during somatic rearrangement in developing T lymphocytes. This, combined with the extraordinary polymorphism of HLA class I and II on antigen-presenting cells, enables the human immune system to respond to almost any pathogen. A smaller population of circulating T cells expresses the γδ TCR, for which antigen recognition is not dependent on HLA class I or II.

Some HLA class I allotypes also serve as KIR ligands, which are primarily expressed on NK cells and are major actors of innate immunity and reproduction. KIRs are encoded by a highly polymorphic gene family that forms two haplotype groups, *A* and *B*, with different gene content. Most *KIR B* haplotypes encode activating KIRs, and *KIR A* haplotypes encode mostly inhibitory KIRs. The competing pressures due to the demands of reproduction and immunity drive the coevolution of *HLA* class I and *KIR* genes as an integrated system. Extensive genetic studies show how their combination influences resistance to infection, susceptibility to autoimmunity, pregnancy disorders, and outcomes of hematopoietic stem cell transplantation. This body of investigation is consistent with balancing selection maintaining the exceptional polymorphism of the *KIR* and *HLA* systems and the balance between *KIR A* and *KIR B* haplotypes in every human population.

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