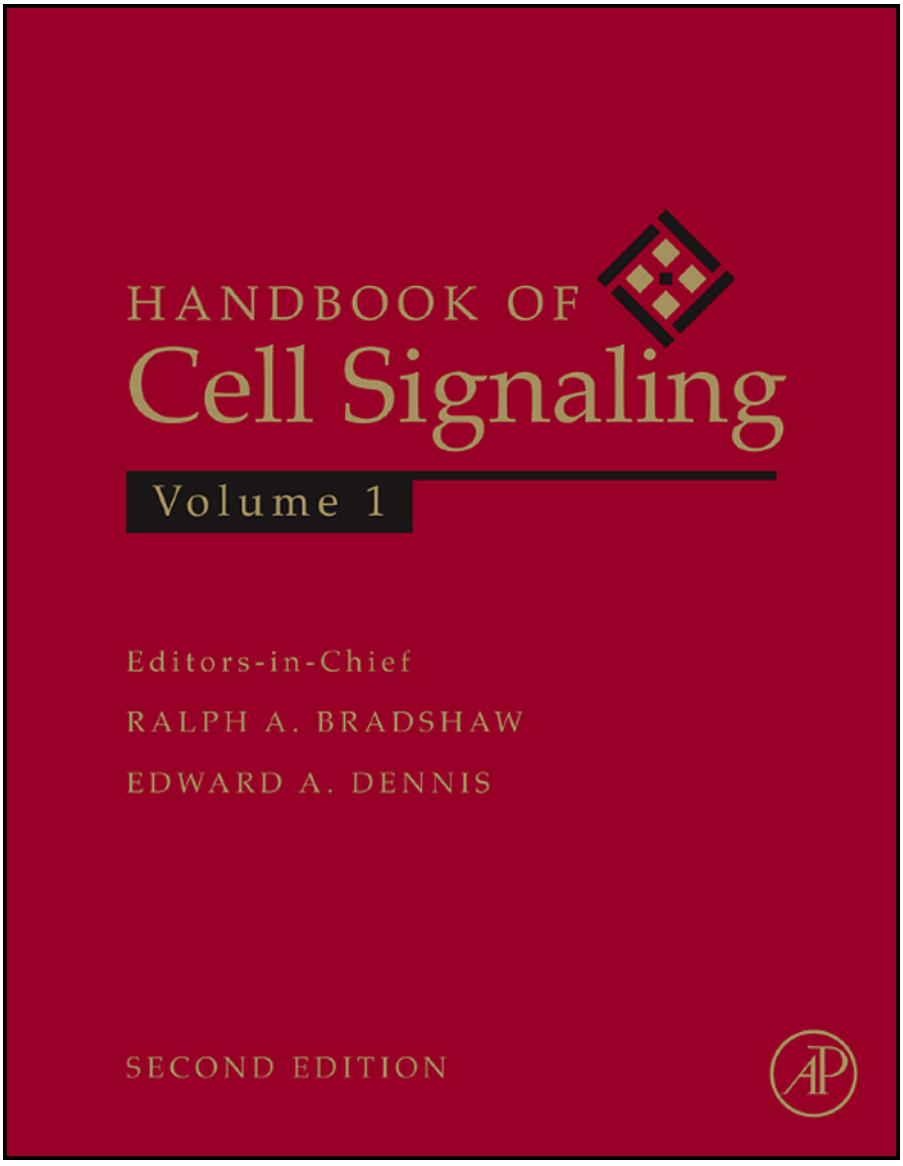

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Chapter 12

NK Receptors

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IMMUNORECEPTORS

Recognition events between the archetypical $\alpha\beta$ receptors on T cells (TCRs) and processed peptide fragments of endogenous proteins, presented on target cell surfaces as complexes with major histocompatibility complex (MHC) class I proteins, ultimately mediate activation of T cell cytotoxic responses by the cellular arm of the adaptive immune system [1]. MHC class I proteins are integral-membrane, heterodimeric proteins with ectodomains consisting of a polymorphic heavy chain, comprising three extracellular domains (α1, α2 and α3), associated with a non-polymorphic light chain, β_2-microglobulin (β_2-m) [2]. The α1 and α2 domains together comprise the peptide- and TCR binding "platform" domain; the α3 and β_2-m domains have C-type immunoglobulin (Ig) folds. Crystal structures of TCR/MHC complexes show that the TCR variable domains sit diagonally on the MHC platform domain, making contacts to the peptide and the MHC α1 and α2 domains (Figure 12.1) [3, 4]. Binding studies show that the equilibrium dissociation constants for these interactions range from one to tens of micromolar; the strength of these interactions, including consideration of kinetic and thermodynamic components, are directly correlated with output signal strength [5]. TCR/MHC binding is also highly degenerate, with any TCR capable of recognizing a range of peptides, often in complexes with different MHCs, through "induced-fit" interactions [6, 7].

NATURAL KILLER CELLS

Surveillance against cells undergoing tumorigenesis [8–13] or infection by viruses [14, 15] or internal pathogens [16, 17] is provided by natural killer (NK) cells, components of the innate immune system, thus helping to provide "covering fire" during the period that responses by the adaptive immune system are gearing up [18, 19]. NK cells are defined as $CD56^+/CD16^+$ cells comprising 10–20 percent of PBMC. NK cells also act to regulate innate and acquired immune responses through the release of various immune modulators, chemokines and cytokines, such as tumor necrosis factor α, interferon γ, MIP-1 and RANTES. Unlike T cells, which clonally express unique TCRs, NK cells function through a diverse array of cell-surface inhibitory and activating receptors with varying specificities.

Many NK cell surface receptors (NKRs) are specific for classical (such as HLA-A, -B and -C in humans) and non-classical (such as HLA-E in humans) MHC class I proteins, and occur in paired activating and inhibitory isoforms [20–22]. Different NKRs, with different MHC class I specificities, are expressed on overlapping, but distinct, subsets of NK cells in variegated patterns–where the strength of the inhibitory signals may be stronger than stimulatory signals. Thus, NK cell effector functions are regulated by integrating signals across the array of stimulatory and inhibitory NKRs engaged upon interaction with target cell surface NKR ligands ("KIR-mismatch") [21–23], resulting in the elimination of cells with reduced or altered MHC class I expression ("missing self"), a common consequence of infection or transformation [24, 25]. The developmental mechanisms that govern NKR expression patterns are still not fully understood, but NK cells that express an inhibitory receptor specific for self MHC class I proteins become "licensed", or functionally competent, while those lacking such a receptor are rendered functionally inert [26]. Other NKRs, such as human and murine NKG2D, recognize divergent MHC class I homologs (ULBPs [27], MICA and MICB in humans [28], and RAE-1 and H60 in mice [29, 30]) not involved in conventional peptide antigen presentation. Inhibitory receptors transduce signals through recruitment of tyrosine phosphatases, such as SHP-1 and SHP-2, and

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contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic domains [31, 32]. Activating receptors associate with immunoreceptor tyrosine-based activation motif (ITAM) -bearing adaptor proteins, either DAP12 [33] or DAP10 [34, 35], through a basic residue in their transmembrane domain. Spontaneous NK effector functions can be activated through triggering receptors, including NKG2D, DNAM-1, and natural cytotoxicity receptors (NCRs: NKp30, NKp44, NKp46); alternatively, NK-mediated antibody-dependent cellular cytotoxicity (ADCC) can be directed against opsonized target cells through antibody Fc/CD16 interactions [18, 36–38]. NKR/ligand affinities span considerable ranges, from hundreds of micromolar to tens of nanomolar (Table 12.1), both within and between NKR families, suggesting signaling mechanisms that respond differentially, comparable to TCRs, likely impacting both activation and developmental pathways. NKRs also display widely varying degrees of specificity, from many KIRs, where binding is determined by the identity of a single residue, to NKG2D, which binds a range of highly polymorphic, structurally divergent ligands.

NKRs can be divided into two broad groups based on structural homologies [39, 40], with some families differentially represented across species. The first group includes

TABLE 12.1 Cell-surface NK receptor/ligand interactions

Type	Receptor	Polymorphism	Signal (+/−)	Ligand	K_D	Ref.	Structures available?
KIRs							
	KIR2DL1-5	High	−	1: HLA-C^{K80}	15−7 μM	[69]	Yes
	(CD158a–f)			2–3: HLA-C^{N80}			
				4: HLA-G			
				5: ?			
	KIR2DS1-5	High	+	1: HLA-C^{K80}	>50−23 μM	[69]	Yes
	(CD158g–j)			2: HLA-C^{N80}			
				3–5: ?			
	KIR3DL1-3	High	−	1: HLA-Bw4	?		No
	(CD158e1, k, z)			2: HLA-A3, -A11			
	KIR3DS1	High	+	?	?		No
	(CD158e2)						
	LILRs	High/low	+/−	MHC class Ia & Ib	100−15 μM	[70]	Yes
	(LIRs, ILTs, CD85)			CMV UL18	2 nM/14 μM	[53]	
KLRs							
	NKG2A/B-CD94	Low	−	Human:	20−0.7 μM	[67, 71]	Yes*
				HLA-E	(varies with peptide)		
				Murine:			
				Qa-1			
	NKG2C/E/H-CD94	Low	+	Human:	120−0.7 μM	[67, 72]	No
				HLA-E	(varies with peptide)		

(*Continued*)

TABLE 12.1 (Continued)

Type	Receptor	Polymorphism	Signal (+/−)	Ligand	K_D	Ref.	Structures available?
				Murine:			
				Qa-1			
	NKG2D	Low	+	Human:			Yes
				MIC-A/B	0.9−0.3 μM	[63]	
				ULBPs	4.0−1.1 μM	[73]	
				Murine:	1.9−0.35 μM	[74]	
				RAE-1α–δ	0.028 μM	[75]	
				RAE-1ε	0.02 μM	[75]	
				H60		[73, 74]	
	Ly49A-W	Low	+/−	MHC class Ia, ?	100−10 μM	[58, 76]	Yes
				(CMV m157)	0.2 μM	[60]	
NCRs							
	NKp30	Low	+	?			No
	NKp44	Low	+	?			Yes
				(Viral HA?)			
	NKp46	Low	+	?			Yes
				(Viral HA?)			
	NKp80	Low	+	?			No
	CD2	Low	+	LFA-2			Yes
	CD16	Low	+	IgG			Yes
	CD59	Low	+	?			Yes
	2B4	Low	+	CD48			Yes
	(CD244)						
	DNAM-1	Low	+	Nectin-2 *(CD112)*			No
	(CD226)			PVR *(CD155)*			
	LFA-1	Low	+	ICAM			Yes
	TLRs	Low	+	PAMPs			Yes
				(dsRNA, LPS,			
				flagellin, etc.)			

*Alternate nomenclature is italicized within parentheses; *: Kaiser* et al.*, personal communication.*

the killer cell Ig receptors (KIR, restricted to NK cells) and the leukocyte Ig-like receptors (LILR, found on many cell types), and consists of type I transmembrane glycoproteins with ectodomains containing tandem Ig domains. The second group, including the rodent Ly49 receptor family and the CD94/NKG2x and NKG2D receptor families found in primates and rodents, comprises homo- and heterodimeric type II transmembrane glycoproteins containing C-type lectin-like NK receptor domains (CTLDs) [41]. Ongoing X-ray crystallographic analyses continue to detail NKR/ligand interactions (Figure 12.1).

IG-TYPE NK RECEPTORS: KIR

Two crystal structures of complexes between inhibitory KIR family NKRs and their MHC class I ligands, KIR2DL2/HLA-Cw3 [42] and KIR2DL1/HLA-Cw4 [43], show that the receptor binds in a 1:1 complex with HLA-C, making contacts to both the α1 and α2 platform domains and the carboxy-terminal end of the bound peptide (Figures 12.1, 12.2). [KIR receptor nomenclature identifies the number of Ig domains (2D(omains) or 3D, specific for HLA-C or HLA-A/B respectively), and whether the receptor is a long (L) form, containing ITIM repeats, or a short (S) form, interacting with ITAM-containing adaptor proteins.] Both complexes have interfaces showing both significant shape and charge complementarity, with the N-terminal KIR domains interacting primarily with the α1 domains of HLA-C, the C-terminal KIR domains contacting the α2 domains, and with additional contacts provided by the interdomain KIR linker peptides (the "elbow"). The kinetics of binding, rapid on and off rates, are consistent with interactions dominated by charge–charge interactions.

Despite a high degree of conservation of binding surface residues between both KIR2DL2 and KIR2DL1, and HLA-Cw3 and -Cw4, few actual intermolecular interactions are conserved. This recognition flexibility is accomplished through altered side-chain conformations. KIR2D receptors distinguish between HLA-C allotypes on the basis of the residue at position 80: KIR2DL1 recognizes lysine and KIR2DL2 recognizes asparagine, and this

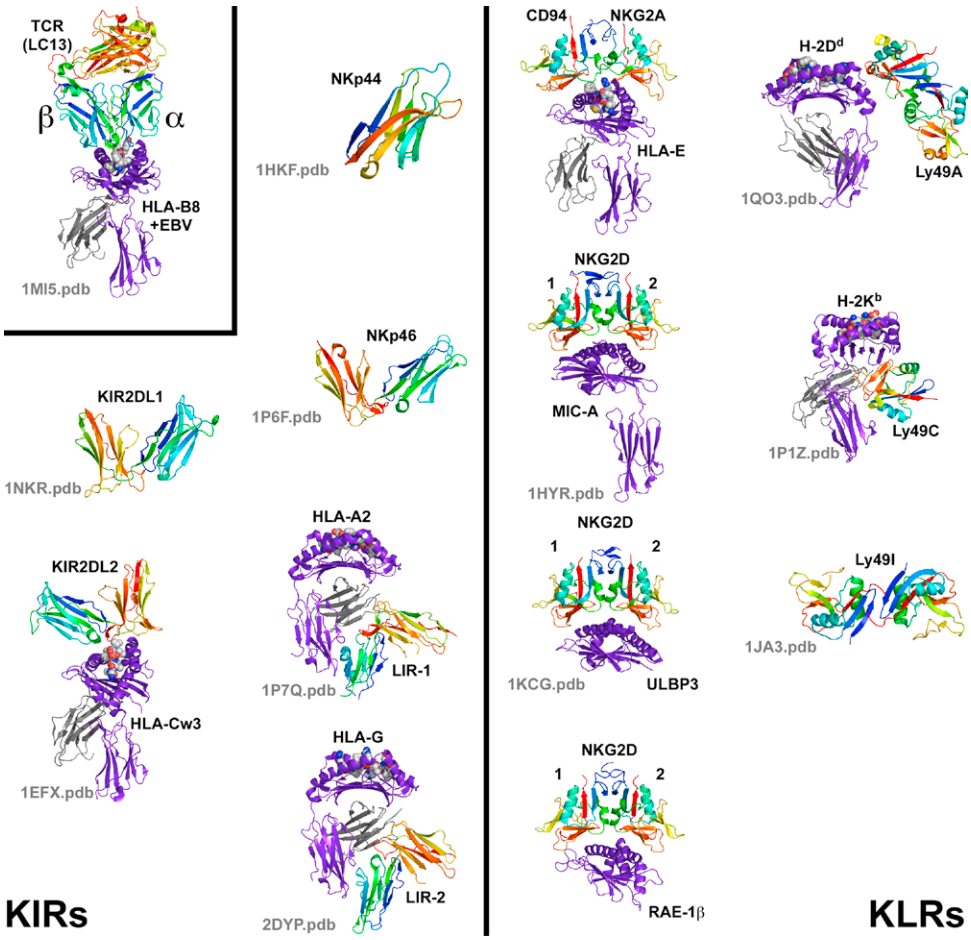

FIGURE 12.1 Ribbon representations of an αβ TCR/MHC class I complex (upper left) and several NKR and NKR/ligand complex structures are shown. PDB accession codes for the coordinate files used to generate the figure are indicated. Only one half of the 1:2 Ly49C:MHC complex is shown, for simplicity.

specificity is conferred by the identity of the residue at position 44 in the receptor. In KIR2DL1, Lys80 is shape- and charge-matched to a distinct pocket on the surface of the receptor; while Asn80 is sensed through a direct hydrogen bond in the KIR2DL2 complex. Additional structures for isolated KIRs are also available: KIR2DL1 [44], KIR2DL2 [45], KIR2DL3 [46] and KIR2DS2 [47].

OTHER IG-TYPE RECEPTORS ON NK CELLS

Several structures are available for isolated NCRs (NKp44 [48] and NKp46 [49, 50]), but little is currently known about their ligands or the details of NCR/ligand interactions. While LILRs contribute significantly to NK function and are subverted through viral decoys like the MHC class I homolog CMV UL18 [51], they are expressed on many cell types and are, therefore, not a focus of this review. Structures are available for isolated LILRs (LILRA5 [52], LILRB1 [53]) and for the LILRB1/HLA-A2 [54] and LILRB2/HLA-G [55] complexes, which show that the receptor Ig-like ectodomains interact with MHC class Ia and Ib ligands in a similar, peptide-independent manner (Figure 12.1), contacting mostly β_2-m and, to a lesser extent, the MHC class I α3 domain. While neighboring to an extent that would result in competition, the Ly49C- and LILR binding sites on MHC class I proteins are distinct.

C-TYPE LECTIN-LIKE NK RECEPTORS: LY49A

Ly49A is a disulfide-linked, symmetric, homodimeric, CTLD-type NKR that is specific for the murine MHC class I protein H-2D^d (the human ortholog is non-functional) [56]. The crystal structure of the D^d/Ly49A complex [57] shows D^d homodimers binding to two distinct sites on the MHC protein (Figure 12.2). The first binding site positions Ly49A on the D^d platform domain, contacting both α1 and α2 and the N-terminal end of the bound peptide–the opposite end from where KIR2D binds. The second binding site positions Ly49A in the cleft between the underside of the platform domain (the top being the peptide and TCR binding surface), the α3 domain and β_2-m. The second site is considerably more extensive than site #1, though less shape-complementary and less dominated by charge–charge interactions, and is likely to be the immunologically relevant interaction on the basis of subsequent mutagenesis studies. Site #2 also overlaps the CD8 binding site on MHC class I proteins (Figure 12.2). As predicted, Ly49A clearly displays a C-type lectin-like fold, though failing to retain any remnant of the divalent cation or carbohydrate binding

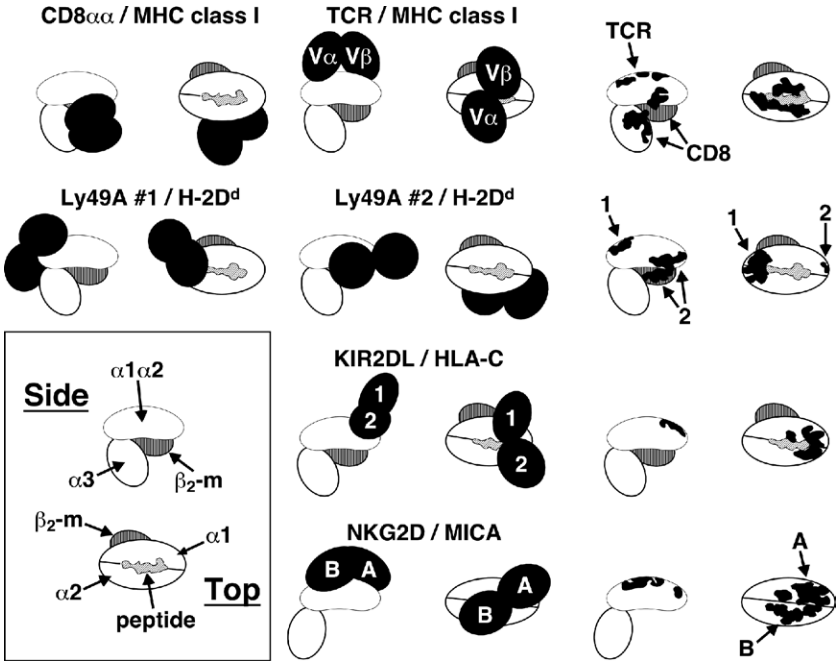

FIGURE 12.2 Structurally-characterized NK receptor/ligand complexes are shown in schematic representations to highlight interaction surfaces. Each row shows two views of a receptor–ligand complex, first showing the organization of domains in the complex (receptor domains in black, labeled where a distinction between domains is significant; MHC class I ligand heavy chains in white and β_2-m in vertical stripes. The arrangement of domains in the ligands is detailed in the inset; the approximate solvent-accessible surface area of the bound peptide, if present, is shown as a cross-hatched area. The right-most columns show approximate footprints of receptors and co-receptors on the ligands as black patches, labeled by receptor component, subsite or domain as appropriate.

sites conserved in true C-type lectins. While the simplest binding mode for a symmetric homodimer is to interact with two monomeric ligands through two identical binding sites, each Ly49A interaction with D^d is with a single monomer because binding of ligand at one site sterically blocks binding at the second, homodimer-related site. Interestingly, the interactions of Ly49C with MHC class I proteins [58] are quite distinct from Ly49A (Figure 12.1). Ly49C makes symmetric interactions with two MHC proteins across the receptor dyad axis of symmetry, not directly contacting the peptide. A crystal structure of isolated Ly49I is also available [59], revealing a distinct dimerization interface from other Ly49 structures. m157 is an MHC class I-like, CMV-encoded decoy ligand that interacts with both Ly49H and I, with much tighter affinities than their true MHC class I ligands (Table 12.1); the structure of m157 shows a compact, minimal MHC molecule which dispenses with peptide and β_2-m association [60].

C-TYPE LECTIN-LIKE NK RECEPTORS: NKG2D

NKG2D is an activating, symmetric, homodimeric, CTLD-type NKR. While highly conserved between primates and rodents, its ligands include very different molecules, both in humans and inrodents. Multiple crystal structures of the receptor alone [61,62] and three complexes (human NKG2D/MICA [63], NKG2D/ULBP3 [64] and murine NKG2D/RAE-1β [65]) show that NKG2D interacts with its MHC class I homologous ligands in a manner very similar to how TCRs interact with classical MHC class I proteins (Figures 12.1, 12.2), even though NKG2D contains CTLDs while TCRs contain Ig domains. NKG2D retains the C-type lectin-like fold seen in Ly49A, with few variations–though the binding surface of NKG2D is much more curved than in Ly49A, matching the more curved surface of its ligands (which do not bind peptides), where the Ly49A and NKG2D binding surfaces encompass overlapping surfaces on the receptors. The interaction surfaces bury considerable solvent-accessible surface area, and are highly shape-complementary, but the human NKG2D/MICA interaction markedly more so than the murine NKG2D/RAE-1 interaction. The reason that the human complex does not bind considerably more tightly than the murine complex (Table 12.1) is likely due to the necessity of ordering a large loop on the surface of MICA concurrent with complex formation, reflected in the unusually slow on-rate for the human complex. Unlike KIR and Ly49A site #1 interactions, the NKG2D binding sites are much less dominated by charge–charge interactions. The stoichiometries of the NKG2D complexes are one homodimer binding to one monomeric ligand. However, unlike Ly49, both homodimer-related binding sites on NKG2D contribute approximately equally to the interactions in both complexes, reflecting a binding site that has evolved to bind multiple target sites without the degree of side-change rearrangements seen in the KIR interactions. The considerable recognition degeneracy of NKG2D, accommodating structurally divergent, polymorphic families of ligands (Table 12.1), is enabled not by a conformationally-plastic binding site (induced-fit recognition), but rather by a "rigid-adaptation" mechanism [7, 66]. The CD94/NKG2A/HLA-E complex structure [68] is quite similar in overall arrangement to NKG2D/ligand and TCR/ligand complexes (Figure 12.1), though peptide sequence differences, which strongly affect receptor affinities, are read out by CD94 and not the NKG2x moiety [67].

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