Chapter 12
Coevolution of Innate and Adaptive Immunity

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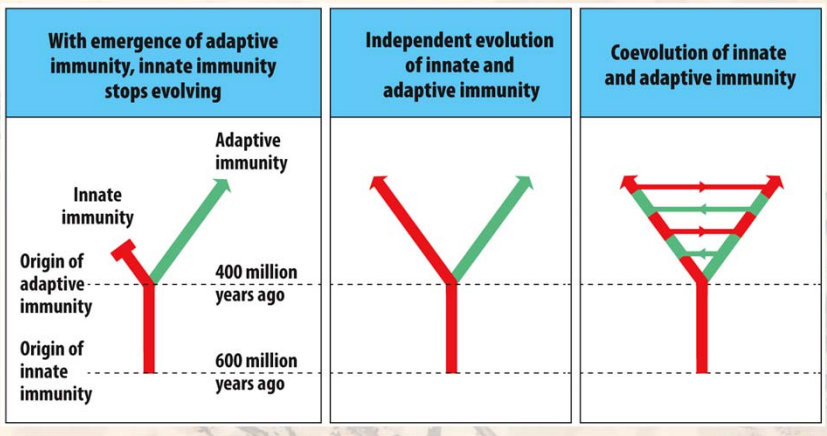

Figure 12.1 Three possible models for the evolution of innate and adaptive immunity. Each panel presents a scenario for the course of evolution of innate and adaptive immunity. The dashed horizontal lines indicate the origin of adaptive immunity some 400 million years ago and the origin of innate immunity at around 600 million years ago. The colored lines denote the components of innate immunity (red) and adaptive immunity (green). Left panel: the evolution of innate immunity slows down and stops after adaptive immunity has emerged and become established. Center panel, innate immunity and adaptive immunity evolve independently and at comparable rates once adaptive immunity has emerged and become established. Right panel: this model is like that in the center panel, except that the evolution of innate and the evolution of adaptive immunity are not independent but interactive. As indicated by the horizontal red and green lines, components of innate immunity continue to be incorporated into adaptive immunity, and components of adaptive immunity become part of innate immunity.

NK cells express a range of activating and inhibitory receptors

Activating NK-cell receptors			
Receptor	**Receptor structure**	**Ligand**	**Ligand structure**
NKp80	Lectin-like	NKp65	Lectin-like
CD94:NKG2C (CD159c)	Lectin-like	HLA-E with bound peptides derived from leader sequences of HLA-A, -B, and -C	MHC class I
KIR2DS1 (CD158h)	Ig-like (2 domains)	C2 epitope of HLA-C	MHC class I
KIR2DL4 (CD158d)	Ig-like (2)	HLA-G	MHC class I
NKG2D (CD314)	Lectin-like	MIC-A, MIC-B, ULBP1–6	MHC class I-like
CD16 (FcγRIIIA)	Ig-like (2)	IgG	Immunoglobulin
2B4 (CD244)	Ig-like (2)	CD48	Ig-like (2 domains)
DNAM-1 (CD226)	Ig-like (2)	Nectin-2 (CD112), Poliovirus receptor (PVR) (CD155)	Ig-like (3)
LFA-1 (CD11a)	Integrin	ICAM-1	Ig-like (5)
NKp30 (CD337)	Ig-like (1)	B7-H6 expressed by some tumors HLA-B-associated transcript 3 (BAT3)	Ig-like (2) Nuclear protein released by tumors
NKp46 (CD335)	Ig-like (2)	Viral hemagglutinins and neuraminidases Membrane protein of malarial parasite	Pathogen-derived antigens of varied structure
†NKp44 (CD336)	Ig-like (2)	Cancer-induced changes to self proteins; mixed-lineage leukemia protein 5 (MLL5)	MLL5 is an intracellular protein that becomes surface-associated in tumors

Figure 12.2 NK cells use many activating and inhibitory receptors to distinguish unhealthy cells from healthy cells. The table gives the name and CD number of the receptor, the type and number of protein domains that form the binding site, the ligand or ligands for the receptor, and the type of protein domain that forms the ligand. The six

UL-binding proteins (ULBPs) are so called because ULBP1, 2, and 6 bind to the cytomegalovirus UL16 protein. They have two extracellular domains resembling the MHC class I α_1 and α_2 domains and are encoded by a gene family on chromosome 6, apart from the MHC.

NK cells express a range of activating and inhibitory receptors

Inhibitory NK-cell receptors			
Receptor	**Receptor structure**	**Ligand**	**Ligand structure**
CD94:NKG2A (CD159a)	Lectin-like	HLA-E with bound peptides derived from HLA-A, -B, and -C leader sequences	MHC class I
KIR2DL1 (CD158a)	Ig-like (2 domains)	C2 epitope of HLA-C having methionine 80	MHC class I
KIR2DL2/3 (CD158b)	Ig-like (2)	C1 epitope of HLA-C having lysine 80, also HLA-B*46 and HLA-B*73	MHC class I
KIR3DL1 (CD158d)	Ig-like (3)	Bw4 epitope of HLA-A and HLA-B having RI/TALR motif at position 79–83	MHC class I
KIR3DL2 (CD158k)	Ig-like (3)	HLA-A*03 and HLA-A*11	MHC class I
LILRB1 (CD85j)	Ig-like (4)	Broad reactivity with HLA class I, strongest binding to HLA-G	MHC class I
†NKp44	Ig-like (2)	Proliferating cell nuclear antigen (PCNA), cancer associated	PCNA is recruited into the NK-cell synapse with tumor target cell and inhibits cell killing

The number in parentheses after Ig-like receptors and ligands is the number of Ig-like domains.
†NKp44 has both ITIM and ITAM motifs (see Section 12-3) and can mediate both activation and inhibition.

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NK cells express a range of activating and inhibitory receptors

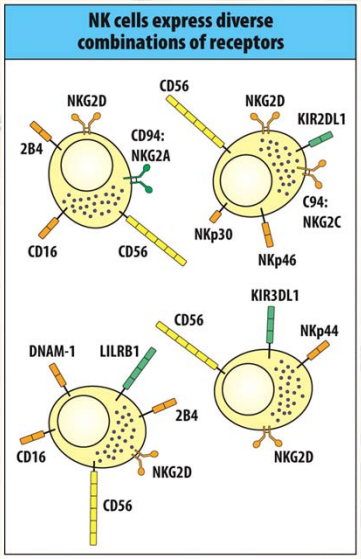


Figure 12.3 NK cells express diverse combinations of receptors. No single NK cell has all of the receptors listed in Figure 12.2 on its surface. Instead, individual NK cells express a subset of the receptors, which produces, as shown here, a diversity of NK-cell phenotypes. All the NK cells are shown expressing CD56, because the expression of this protein in the absence of a T-cell receptor is used to define NK cells (see Section 3-17). All NK cells also express an inhibitory receptor for self-MHC class I. CD94:NKG2A, KIR2DL1, KIR3DL1, and LILRB1 are examples of such receptors.

The strongest receptor that activates NK cells is an Fc receptor

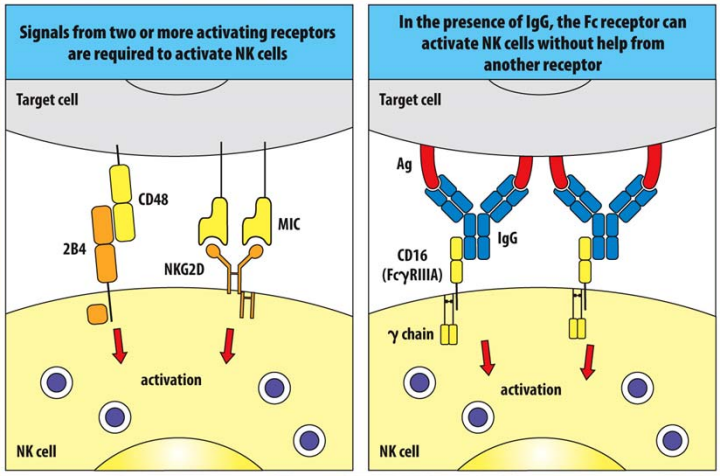


Figure 12.4 Activation of NK cells by receptors of innate and adaptive immunity. Left panel: activation of an NK cell by the 2B4 and NKG2D receptors of innate immunity. Both of these receptors must bind to their respective ligands on the target cell to produce signaling that will activate the NK cell. Right panel: an NK cell being activated by $Fc\gamma RIIIA$ that has bound complexes of cell-surface antigens and antigen-specific IgG molecules. Signals from the Fc receptor alone are sufficient to activate the NK cell.

Many NK-cell receptors recognize MHC class I and related molecules

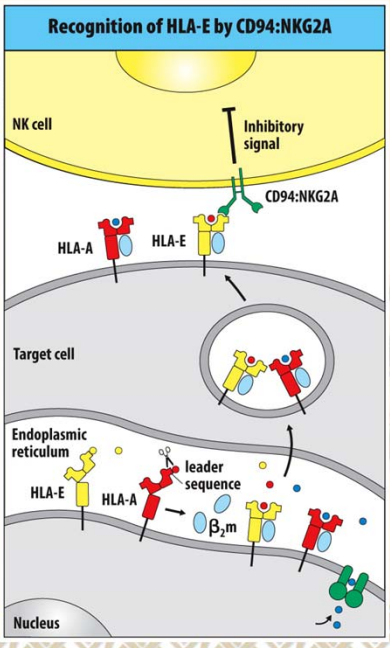


Figure 12.5 CD94:NKG2A recognizes complexes of HLA-E and peptides derived from the leader sequences of HLA-A, -B, and -C. During normal biosynthesis, the leader sequences of HLA-A, -B, and -C are cleaved off in the endoplasmic reticulum. These are further cleaved to give smaller peptides, for which the HLA-E peptide-binding site is highly specific. After binding one of these peptides, HLA-E travels to the cell surface and is recognized by the inhibitory NK-cell receptor CD94:NKG2A. For healthy target cells expressing normal levels of HLA-E, the inhibitory signals transduced by CD94:NKG2A tell the NK cell not to respond to the target cell. β_2m, β_2-microglobulin.

Many NK-cell receptors recognize MHC class I and related molecules

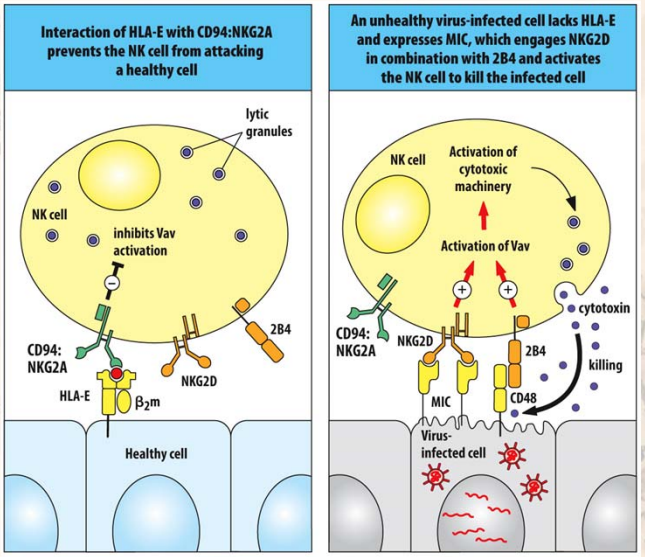


Figure 12.6 Signals from inhibitory receptors block the signaling pathways of NK-cell activation.

Immunoglobulin-like NK-cell receptors recognize polymorphic epitopes of HLA-A, HLA-B, and HLA-C

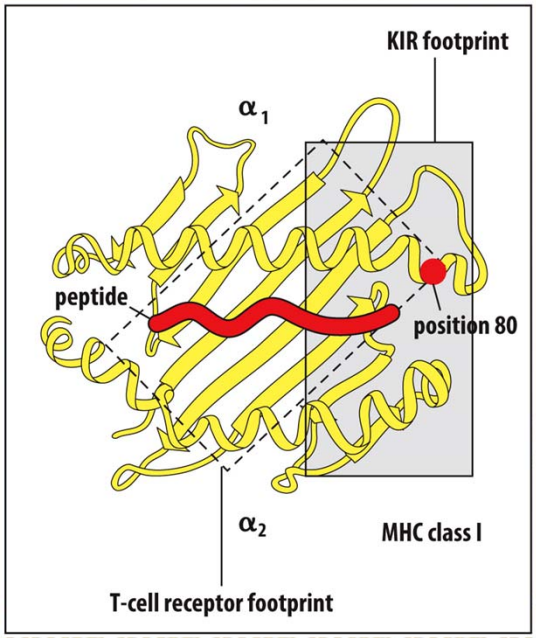


Figure 12.7 Killer-cell immunoglobulin-like receptors (KIRs) bind to the same face of the MHC class I molecule as the T-cell receptor. The ribbon diagram shows the structure of the α_1 and α_2 domains of an MHC class I molecule. The tops of the two α helices and of the bound peptide in the groove between them form the face that interacts with T-cell receptors and KIRs. The rectangle outlined with a dashed line shows the part of the MHC class I face that interacts with T-cell receptors; the rectangle outlined with a solid line shows the part that interacts with KIR.

Immunoglobulin-like NK-cell receptors recognize polymorphic epitopes of HLA-A, HLA-B, and HLA-C

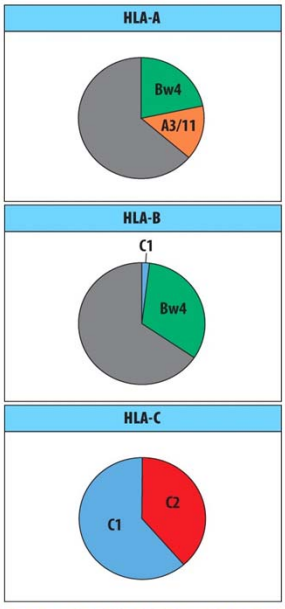


Figure 12.8 Distribution among the HLA-A, -B, and -C allotypes of the four epitopes recognized by KIRs. The pie charts in the top three panels show the proportion of HLA-A, -B, and -C allotypes that carry the A3/11, Bw4, C1, and C2 epitopes. Two divergent HLA-B allotypes, HLA-B*46 and HLA-B*73 carry the C1 epitope. The bottom panel shows the KIR that recognizes each of the four epitopes and also HLA-G, and whether they have activating or inhibitory signaling function.

Cognate KIRs		
KIR	Epitope specificity	Signal
3DL1	Bw4	Inhibitory
3DL2	A3/11	Inhibitory
2DL1	C2	Inhibitory
2DL2/3	C1	Inhibitory
2DS1	C2	Activating
2DL4	HLA-G	Activating

NK cells are educated to detect pathological change in MHC class I expression

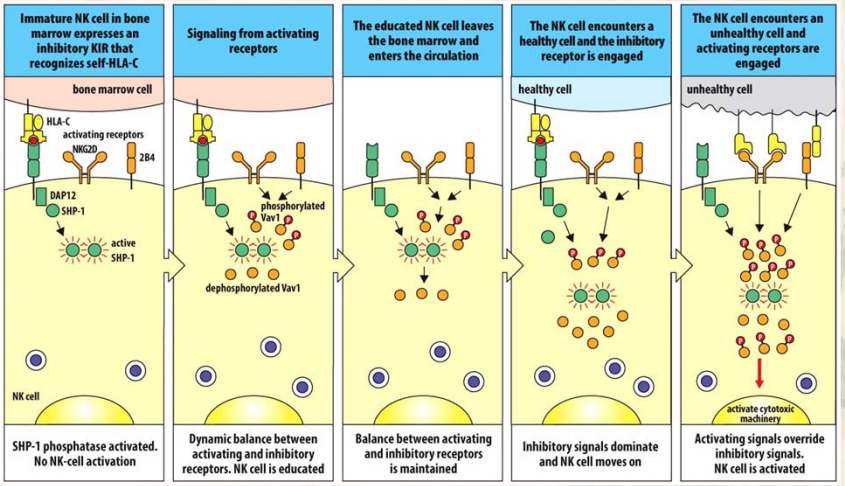


Figure 12.9 NK-cell education involves balancing the signaling pathways for inhibition and activation. The signals coming from the inhibitory receptors activate SHP-1 (first panel), which blocks the activation pathways by dephosphorylating Vav (second panel). This balancing of activation and inhibition is the education that matures the NK cell, which then leaves the bone marrow to enter the circulation and tissues (third panel). This balance is maintained when the NK cell interacts with healthy cells (fourth panel), but when an unhealthy cell is encountered (fifth panel), the inhibitory signals decrease and the activating signals increase, because ligands for the activating receptors are expressed on the unhealthy cell. The NK cell becomes fully activated and the unhealthy cell will soon be killed.

NK cells are educated to detect pathological change in MHC class I expression

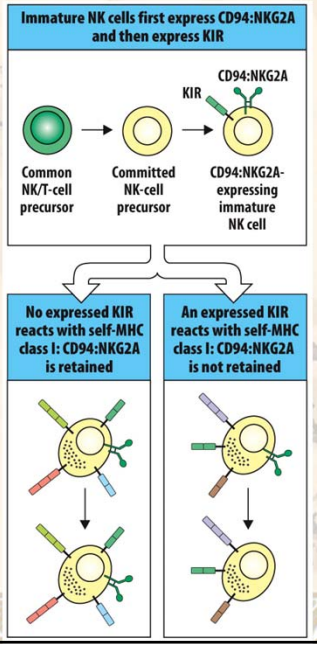


Figure 12.10 NK-cell acquisition of inhibitory receptors for self-MHC class I. In NK-cell development, the inhibitory receptor CD94:NKG2A, with broad MHC class I specificity is first expressed. Subsequently, the KIR genes are expressed. NK cells express different numbers and combinations of KIRs. If none of the expressed KIRs recognizes self-MHC class I, the NK cell retains expression of CD94:NKG2A as its only inhibitory receptor for self-MHC class I (bottom left panel). If one of the KIRs expressed by the NK cell recognizes self-MHC class I, then the cell usually, but not always, turns off CD94:NKG2A expression and uses KIR as the inhibitory receptor for self-MHC class I.

NK cells are educated to detect pathological change in MHC class I expression

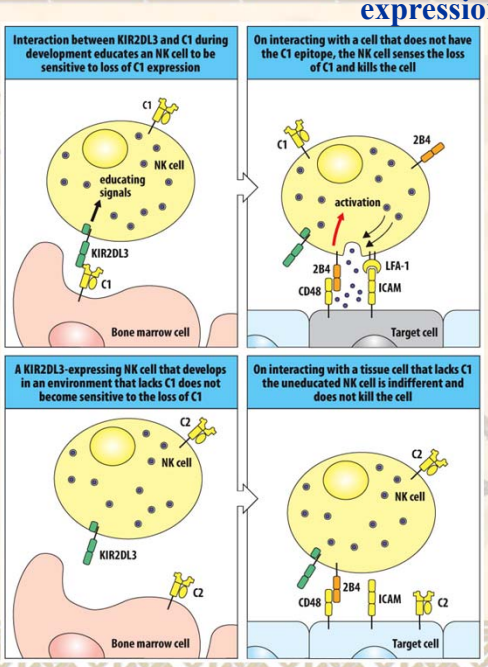


Figure 12.11 NK cells are educated by inhibitory receptors that recognize self-MHC class I. The upper panels show the education by C1 of an NK cell that expresses the C1-specific inhibitory receptor KIR2DL3. The interaction of C1 with KIR2DL3 develops an inhibitory signal that calibrates the NK cell to know what degree of inhibition is to be expected from healthy cells expressing the C1 epitope (left panel). The NK cell can then respond to tissue cells that lack C1. In the laboratory experiment shown in the right panel, the NK cell is killing cells isolated from a family member who does not have C1. Adhesive interactions between LFA-1 on the NK cell and ICAM on the target cell are crucial for the NK cell's response. The lower panels show the lack of education of a developing NK cell that has KIR2DL3 as the only inhibitory receptor in a person who does not have the epitope C1, only C2. As KIR2DL3 does not find C1, the NK cell receives educating inhibitory signal (left panel). If the NK cell subsequently interacts with self tissue cells that lack C1 it does not respond.

Different genomic complexes encode lectin-like and immunoglobulin-like NK-cell receptors

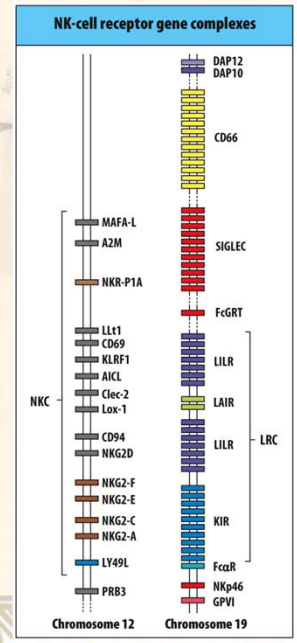


Figure 12.12 Many NK-cell receptors are encoded by genes in one of two genetic complexes. The natural killer complex (NKC) on human chromosome 12 encodes lectin-like NK-cell receptors, whereas the leukocyte receptor complex (LRC) on chromosome 19 encodes NK-cell receptors that are members of the immunoglobulin superfamily. The LRC comprises the killer-cell immunoglobulin-like receptor (KIR), the leukocyte immunoglobulin-like receptor (LILR), and the leukocyte-associated immunoglobulin-like receptor (LAIR) gene families. Flanking the LRC are genes encoding other immunoglobulin-like molecules of the immune system, including the NKp46 receptor of NK cells, and the DAP10 and DAP12 signaling adaptor molecules that transduce signals from activating NK-cell receptors. Figure based on data courtesy of John Trowsdale.

Different genomic complexes encode lectin-like and immunoglobulin-like NK-cell receptors

Similarities between human KIR and mouse Ly49 receptors
Recognize polymorphic determinants of MHC class I molecules
Educate NK cells to respond to missing self-MHC class I
Comprise polymorphic inhibitory receptors and non-polymorphic activating receptors
Use the same activating and inhibiting pathways of signal transduction
Exhibit variegated expression by which NK cells express different numbers and combinations of receptors
Organization of the gene families into two regions of gene-content variation bounded by conserved framework genes

Figure 12.13 Similarities between human KIRs and mouse Ly49 receptors. Although human KIRs have ligand-binding sites made from immunoglobulin-like domains and mouse Ly49 receptors are made from lectin-like domains, their biological properties and function are remarkably similar. This independent convergence on similar function is called convergent evolution.

Human KIR haplotypes uniquely come in two distinctive forms

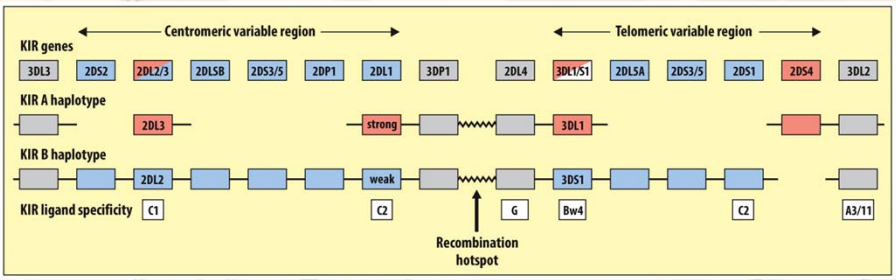


Figure 12.14 Organization of the KIR genes and the two groups of KIR haplotypes. Each box corresponds to a different KIR gene. The top line shows the 15 KIR genes and their order in the locus. The next two lines of boxes depict typical KIR A (second line) and KIR B (third line) haplotypes. Framework genes are shaded gray; genes or alleles that are typical of KIR A and B haplotypes are colored red and blue, respectively. The white boxes in the bottom line show the HLA class I epitope recognized by that particular KIR. The site of recombination between the centromeric and telomeric regions of variable gene content is indicated by the jagged line. The 2DL1 alleles of the A haplotype encode strong inhibitory C2 receptors, whereas the 2DL1 alleles of the B haplotypes encode weak inhibitory C2 receptors.

Cytomegalovirus infection induces proliferation of NK cells expressing the activating HLA-E receptor

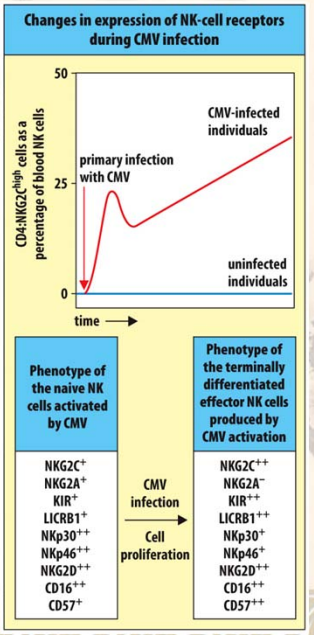


Figure 12.15 CMV infection causes the proliferation of NK cells expressing CD94:NKG2C, an activating receptor that recognizes HLA-E. NK cells expressing the activating HLA-E receptor CD94:NKG2C are rare in human blood and they have the phenotype shown in the lower left panel. The superscripts ++, +, and – denote cells with high, low, or no expression of the given cell-surface marker. When these cells are activated to proliferate and differentiate by CMV infection, they acquire the phenotype shown in the lower right panel. The graph in the upper panel shows the expansion in number of CD4:NKG2C^{++} cells over time after the start of CMV infection.

Interactions of uterine NK cells with fetal MHC class I molecules affect reproductive success

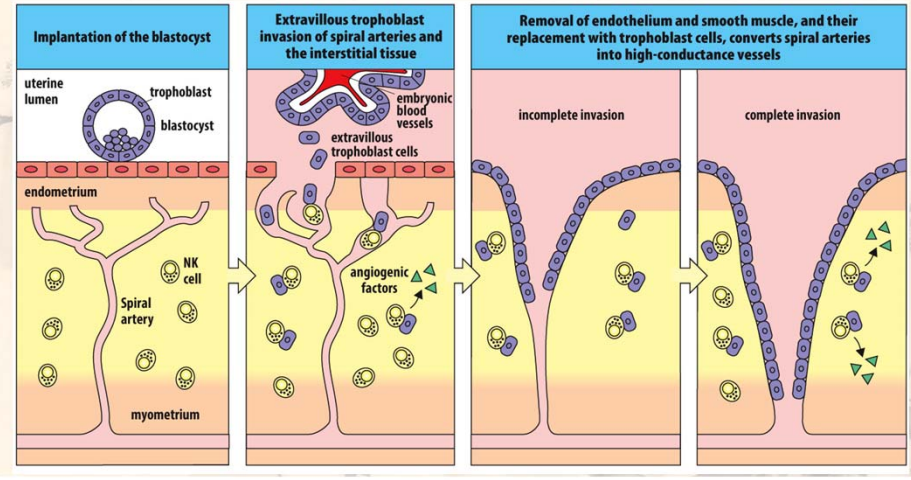


Figure 12.16 Uterine NK cells cooperate with fetal extravillous trophoblast cells to provide the placenta with an adequate supply of maternal blood. The first panel shows the state of the uterine wall before the blastocyst implants. The second panel shows a later stage at which the placenta is developing and the embryo has developed its own blood supply. Extravillous trophoblast cells have left the main layer of trophoblast and invaded the uterine tissue, where they interact with and are controlled by uterine NK cells. The third and fourth panels show the widening of arteries in the uterine wall by the actions of the extravillous trophoblast cells under the control of NK cells.

Interactions of uterine NK cells with fetal MHC class I molecules affect reproductive success

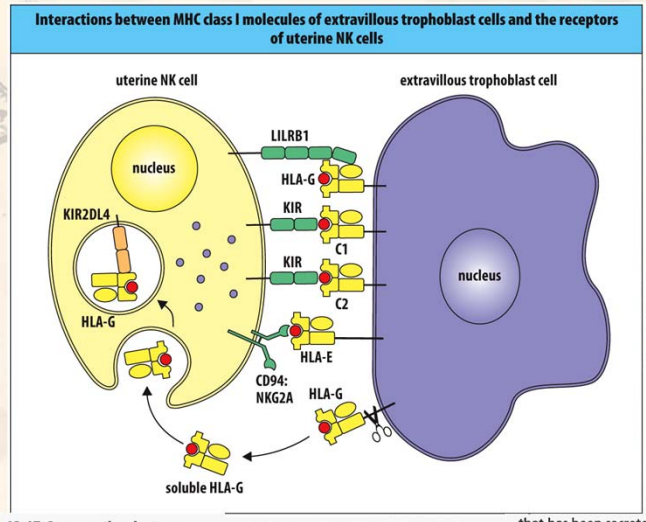


Figure 12.17 Cooperation between extravillous trophoblast cells and uterine NK cells is controlled by fetal HLA class I molecules interacting with maternal NK-cell receptors. Five NK-cell receptors recognize HLA class I molecules of fetal extravillous trophoblast cells. KIR2D2/3 recognizes the C1 epitope of fetal HLA-C, whereas KIRD2S1 and KIR2DL1 recognize the C2 epitope. CD94:NKG2A recognizes HLA-E, and LILRB1 recognizes cell-surface HLA-C, -E, and -G, but HLA-G is the strongest ligand. KIR2DL4 recognizes soluble HLA-G that has been secreted by extravillous trophoblast cells and taken up into endosomes by the NK cells.

Interactions of uterine NK cells with fetal MHC class I molecules affect reproductive success

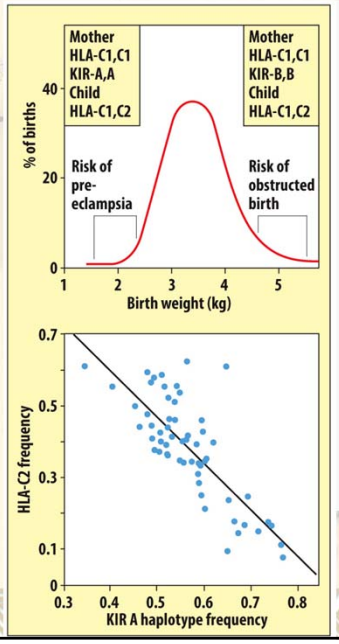


Figure 12.18 Certain combinations of fetal HLA-C and maternal KIR haplotypes are associated with complications of pregnancy and birth. Top panel: human birth weights form a normal distribution with a mean value of 3.4 kg. Two complications that are correlated with birth weight and with KIR and HLA-C haplotype are pre-eclampsia and obstructed birth. Pre-eclampsia is a condition of the last trimester of pregnancy and is associated with an underweight fetus and high maternal blood pressure. The genetic combination associated with pre-eclampsia is the mother being homozygous for KIR A and HLA-C bearing C1 and the fetus inheriting C2-bearing HLA-C from the father. Obstructed birth is the condition when the baby is too large and gets stuck in the birth canal while the mother is giving birth. The genetic combination associated with obstructed birth is when the mother is homozygous for KIR B and HLA-C bearing C1 and the fetus is heterozygous for HLA-C bearing C1 and C2. Both pre-eclampsia and obstructed birth can be avoided by using Cesarian section to deliver the baby. Pre-eclampsia can also be prevented from leading to eclampsia by inducing premature birth. Bottom panel: how the frequency of the C2 epitope in human populations is inversely correlated with the frequency of KIR A haplotypes. Each data point corresponds to a different human population. Included are 5 African, 23 Asian, 23 European, 1 Oceanian, 2 Amerindian, and 5 Hispanic populations. This correlation reveals the strong effect of natural selection due to pre-eclampsia and eclampsia. As a result of that selection, the frequency of pregnancies that have the genetic combination associated with pre-eclampsia is much reduced. There seems to have been a less strong selection exerted by obstructed births.

Summary

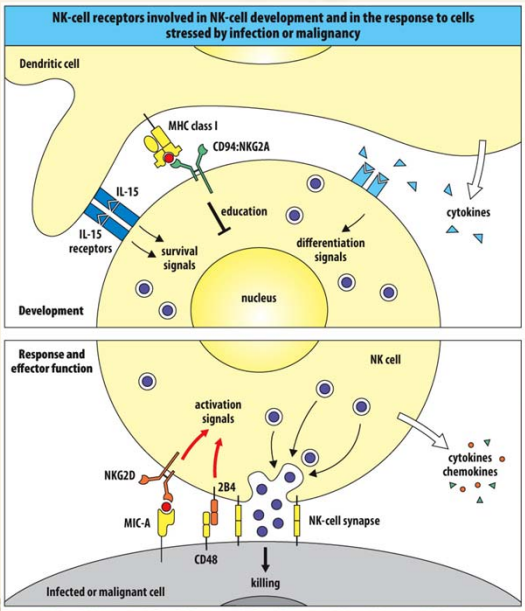


Figure 12.19 Various NK-cell receptors control NK-cell development, response, and effector function. The upper panel shows receptor–ligand interactions involved in NK-cell development. This involves a nurturing interaction with a dendritic cell and NK-cell education, mediated here by CD94:NKG2A. The lower panel shows an NK cell responding to an unhealthy cell. It becomes activated, mobilizes its cytotoxic granules, and kills the target cell. See Chapter 3 for more details of the interactions of NK cells with target cells (Section 3-19), macrophages (Section 3-20) and dendritic cells (Section 3-21).

γ:δ T cells are not governed by the same rules as α:β T cells

Comparison of the similarities and differences between α:β and γ:δ T cells

	α:β T cells	γ:δ T cells
Site of development	Thymus	Thymus
Rearranging receptor genes	α and β genes	γ and δ genes
Germline repertoire of V gene segments	Large	Small
T-cell receptor diversity	Large	Small to medium
Positive selection	Yes	Unknown: probably no
Negative selection	Yes	Unknown: probably yes
Co-receptor	CD4 65% CD8 35%	$CD4^-$ $CD8^-$ ~70% CD8αα ~30% of gut IEL
Target antigens	Peptides presented by MHC class I or class II molecules	Self-proteins resembling MHC class I molecules Non-peptide small molecules presented by MHC class I-like and other cell-surface proteins
Abundance in blood	70% of blood lymphocytes	5% of blood lymphocytes
Abundance in tissues	Relatively rare and transient	Plentiful and resident
Activation	Circulate in inactive form that requires several days of activation	Present in tissues in a form that is quick to respond to infection and other forms of stress
Overall function	Adaptive immunity	Tissue homeostasis: surveillance, protection, and repair

Figure 12.20 Similarities and differences between α:β and γ:δ T cells.

γ:δ T cells in blood and tissues express different γ:δ receptors

Type of γ:δ T cell	Phenotype	
	CD27	CD45RA
Naive	+	+
Effector memory	–	–
Central memory	+	–
Terminally differentiated	–	+

Figure 12.21 The CD27 and CD45RA cell-surface markers are used to differentiate four developmental stages of γ:δ T cells.

γ:δ T cells in blood and tissues express different γ:δ receptors

Tissue	Predominant V gene segment	V(D)J diversity
Thymus	$V_\delta 1$	High
Blood	$V_\gamma 9{:}V_\delta 2$	Intermediate
Spleen	$V_\delta 1$	High
Liver	$V_\gamma 3$ and $V_\delta 1$	High
Gut epithelium	$V_\gamma 3$ and $V_\delta 1$	High
Dermis	$V_\delta 1$	High
Uterus	$V_\delta 1$	High

Figure 12.22 The γ:δ T cells in different tissues are distinguished by their γ:δ T-cell receptors.

γ:δ T cells in blood and tissues express different γ:δ receptors

Inverse correlation between the abundance of γ:δ T cells in the blood and the diversity of α:β T-cell receptor and immunoglobulin V-region genes in different species

	γ:δ T cells: % of blood lymphocytes	Diversity of α:β T-cell receptor V-region genes	Diversity of Ig V-region genes
Human	5%	High	High
Mouse	5%		
Chicken	20%	Low	Low
Rabbit	20%		
Sheep	30%		
Cattle	30%		

Figure 12.23 Mammalian species with higher numbers of blood γ:δ T cells have reduced immunoglobulin and α:β T-cell receptor diversity.

Vγ9:Vδ2 T cells recognize phosphoantigens presented on cell surfaces

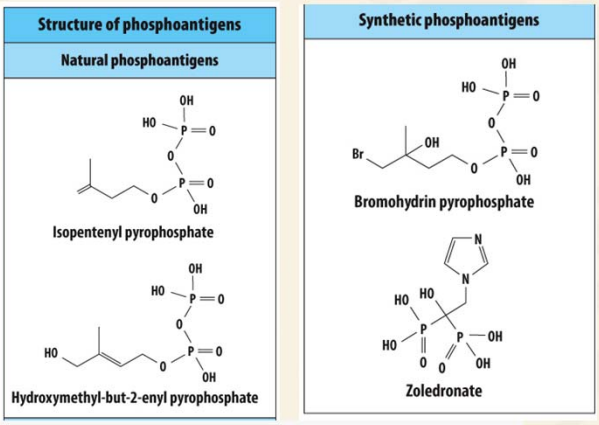


Figure 12.24 $V_\gamma9:V_\delta2$ receptors of blood γ:δ T cells recognize phosphoantigens. All phosphoantigens contain a pyrophosphate group, which is made up of two phosphates. The chemical structures of two natural and two synthetic phosphoantigens are shown here. Isopentenyl pyrophosphate is made by all living organisms. Hydroxymethyl-butenyl pyrophosphate is made by bacteria and some parasites but not by humans. Bromohydrin is a synthetic and potent phosphoantigen used in laboratory experiments to activate γ:δ T cells. Zoledronate is a synthetic phosphoantigen and a licensed drug; when given to osteoporosis patients, it stimulates their $V_\gamma9:V_\delta2$ γ:δ cells to repair eroded bone tissue.

Vγ9:Vδ2 T cells recognize phosphoantigens presented on cell surfaces

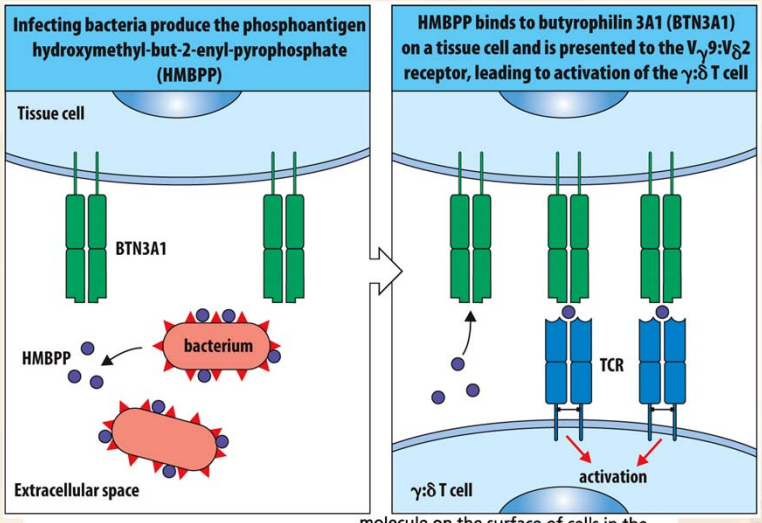


Figure 12.25 Butyrophilin 3A1 on tissue cells binds phosphoantigens and presents them to γ:δ T cells. Bacteria infecting a tissue release the phosphoantigen HMBPP (left panel). HMBPP is bound by the butyrophilin 3A1 molecule on the surface of cells in the infected tissue and is presented to the $V_\gamma9:V_\delta2$ receptors of γ:δ T cells. Signals coming from the T-cell receptor activate the γ:δ cells (right panel).

Vγ4:Vδ5 T cells detect both virus-infected cells and tumor cells

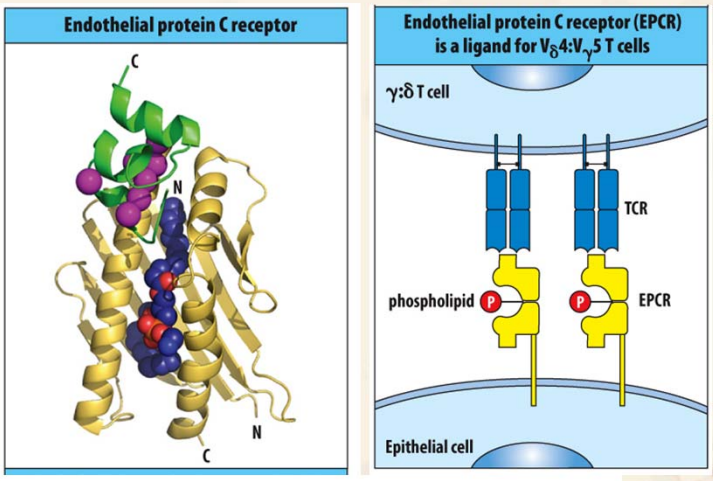


Figure 12.26 The endothelial protein C receptor is a ligand for $V_\gamma4:V_\delta5$ T cells. Upper panel: the endothelial protein C receptor (EPCR) is structurally like the α_1 and α_2 domains of MHC class I. This diagram shows how EPCR (yellow) has a groove that binds a phospholipid antigen (red and blue), not a peptide antigen, and a different site that binds protein C (purple). Lower panel: endothelial protein C is a ligand for $V_\gamma4:V_\delta5$ T cells. Structure courtesy of V. Oganesyan.

Vγ:Vδ1 T-cell receptors recognize lipid antigens presented by CD1d

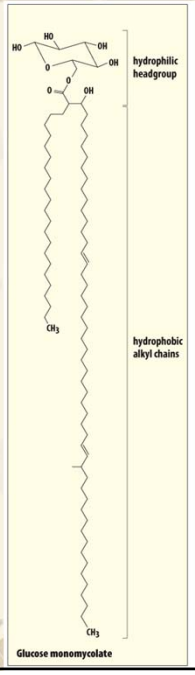


Figure 12.27 The chemical structure of glucose monomycolate, a glycolipid antigen from the bacterium *Mycobacterium phlei*. This glycolipid antigen is part of the cell wall of *M. phlei*. It is presented to α:β T cells by CD1b. Its physical and chemical properties are very different from those of the peptide antigens presented by MHC class I molecules. Because much of the glycolipid antigen is not seen by the T-cell receptor but is hidden in hydrophobic channels in the MHC class I molecule, T cells stimulated by one glycolipid antigen will cross-react with other structurally related lipids that have similar hydrophilic headgroups. *M. phlei* only causes disease for immunocompromised people, showing that most human immune systems are effective at controlling infection by these mycobacteria.

Vγ:Vδ1 T-cell receptors recognize lipid antigens presented by CD1d

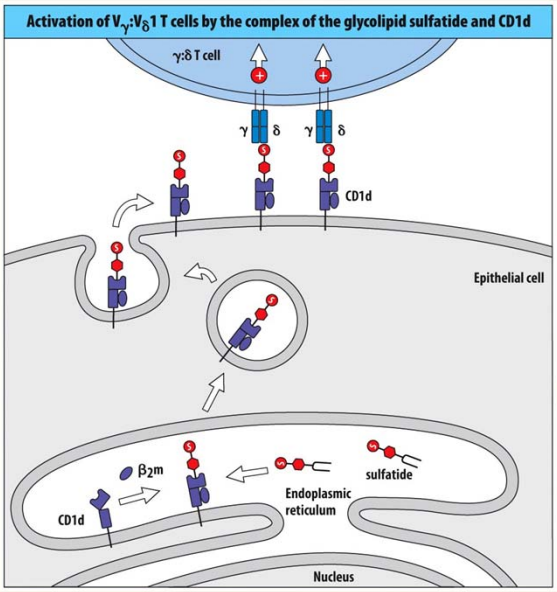
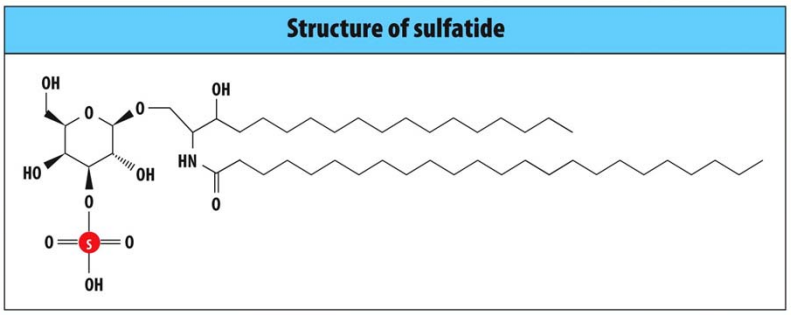


Figure 12.28 CD1d presents glycolipid antigens to the V_γ:V_δ1 receptors of γ:δ T cells. Sulfatide is a glycolipid made by human cells and is abundant in the intestinal epithelium. The upper panel shows sulfatide being bound by CD1d in the endoplasmic reticulum and then transported to the cell surface. There the sulfatide is recognized by the antigen receptor of a V_γ:V_δ T cell. The lower panel shows the chemical structure of sulfatide.

Vγ:Vδ1 T-cell receptors recognize lipid antigens presented by CD1d



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CD1-restricted α:β T cells recognize lipid antigens of mycobacterial pathogens

Mycobacterial lipid antigens are presented by CD1 molecules

Antigen	Antigen-presenting molecule
Diacylsulfoglycolipid	CD1b
Glucose monomycolate	CD1b
Mycolic acid	CD1b
Lipoarabinomannan	CD1b
Lipomannan	CD1b
Phosphatidylinositol mannoside	CD1b
Mannosyl-β-1-phosphomycoketide	CD1c
Didehydroxymycobactin	CD1a

Figure 12.29 Presentation of mycobacterial antigens by CD1 molecules. The CD1 molecules are particularly important in the control and elimination of mycobacterial infections. Mycobacteria are distinguished by a large number of unusual and antigenic glycolipids that are bound by CD1. Examples of such glycolipids and the CD1 molecules that present them are shown here. The structure of glucose monomycolate is shown in Figure 12.27.

CD1-restricted α:β T cells recognize lipid antigens of mycobacterial pathogens

CD1 genes	Tissue distribution: Developing thymocytes	Professional antigen-presenting cells	Other hematopoietic cells	Epithelium	Recognition by T-cell receptors: α:β T-cell receptor	γ:δ T-cell receptor
CD1D	+	+	+	+	+	+
CD1A	+	+	–	–	+	+
CD1C	+	+	–	–	+	+
CD1B	+	+	–	–	+	+
CD1E	–	+	–	–	–	–

Figure 12.30 The CD1 family of proteins that bind lipid antigens. The order of the CD1 genes within the gene family on chromosome 1 is shown on the left. The group 1 CD1 genes, *CD1A*, *CD1B*, and *CD1C*, are together in the center and are flanked on one side by *CD1D*, the group 2 CD1 gene, and on the other side by *CD1E*, the group 3 CD1 gene. The tissue distribution of the five CD1 protein isoforms (CD1a, CD1b, CD1c, CD1d, and CD1e) is given, as is their capacity to present lipid antigens to the receptors of α:β and γ:δ T cells. CD1e is an intracellular lipid-transport protein that facilitates the loading of CD1b and CD1c with lipid antigens but does not itself present antigens to T cells.

CD1-restricted α:β T cells recognize lipid antigens of mycobacterial pathogens

Functional properties of group 1 CD1 molecules	CD1a	CD1c	CD1b
Size of binding site ($Å^3$)	1350	1780	2200
Adaptor protein	None	AP2	AP2 and AP3
Depth of penetration of cell on cycling	Shallow	Intermediate	Deep
Site of lipid transfer	Cell surface Early endosomes	Intermediate endosomes	Late endosomes Lysosomes
State of binding site in absence of lipid	Intact and robust	Collapsed	Collapsed
Chaperoned by CD1e	No	Yes	Yes
Scaffolding lipids	No	No	Yes
Example of antigen	Dideoxymycobactin	Mycoketides	Diacylated sulfoglycolipids Mycolyl lipids

Figure 12.31 Group 1 CD1 molecules have acquired distinctive properties that allow them to bind lipid antigens within different sets of intracellular vesicles. These properties enable the CD1 molecules to scour all types of intracellular vesicles for mycobacterial antigens and to prevent mycobacteria from hiding from the immune defenses in any one type of vesicle.

NKT cells are innate lymphocytes that detect lipid antigens by using α:β T-cell receptors

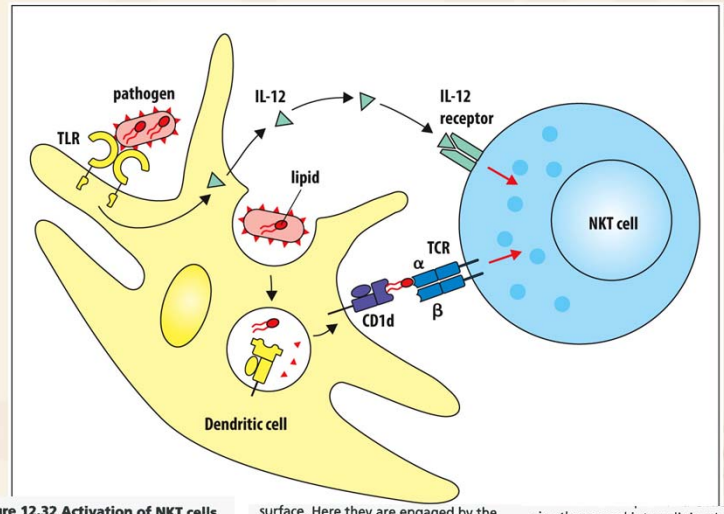

Figure 12.32 Activation of NKT cells requires two signals, one from the T-cell receptor and the other from a cytokine receptor. Uptake of pathogen and its degradation in the endosomes and lysosomes of a dendritic cell in infected tissue enable lipid antigens to be bound by CD1d and taken to the cell surface. Here they are engaged by the NKT cell's α:β T-cell receptor (TCR). This provides the first intracellular signal for NKT-cell activation. On sensing the presence of the pathogen, a Toll-like receptor (TLR) signals the dendritic cell to secrete the cytokine IL-12, which acts on the IL-12 receptor of the NKT cell to give the second intracellular signal for activation.

NKT cells are innate lymphocytes that detect lipid antigens by using α:β T-cell receptors

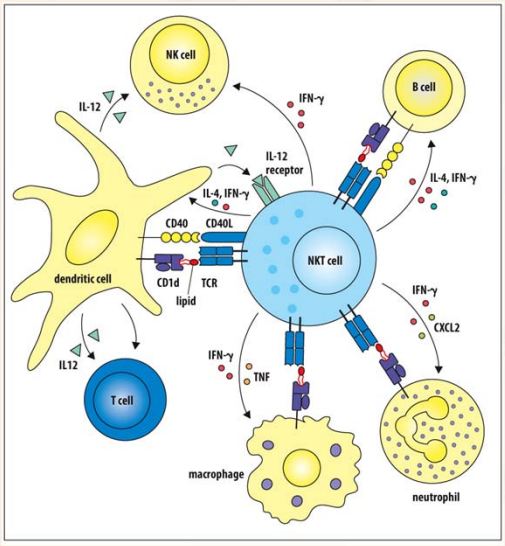

Figure 12.33 In responding to changes in self and microbial lipid antigens, NKT cells orchestrate an immune response through interactions with several different types of cells of innate and adaptive immunity. The NKT cell can have conjugate interactions with the NK cells, dendritic cells, macrophages, and neutrophils of innate immunity and also the B cells of adaptive immunity. Through cytokine secretion, NKT cells can also influence the T cells of adaptive immunity.

Mucosa-associated invariant T cells detect bacteria and fungi that make riboflavin

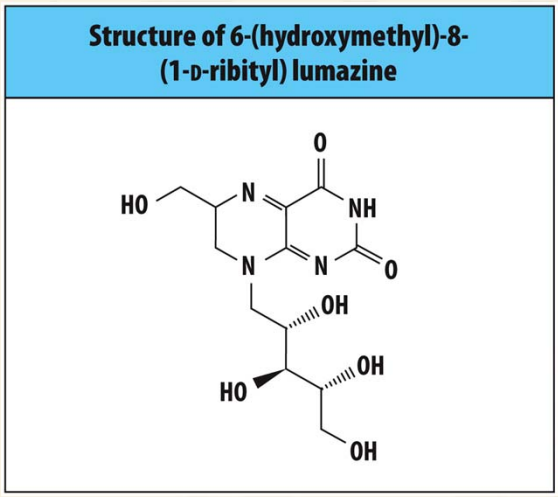

Figure 12.34 Mucosa-associated invariant T (MAIT) cells recognize by-products of the synthesis of riboflavin called pterins. Such substances were first isolated from butterfly wings. Hence the name pterin, which is derived from the Greek word for wing. The chemical structure of the pterin reduced 6-(hydroxymethyl)-8-(1-D-ribityl) lumazine is shown here.

Mucosa-associated invariant T cells detect bacteria and fungi that make riboflavin

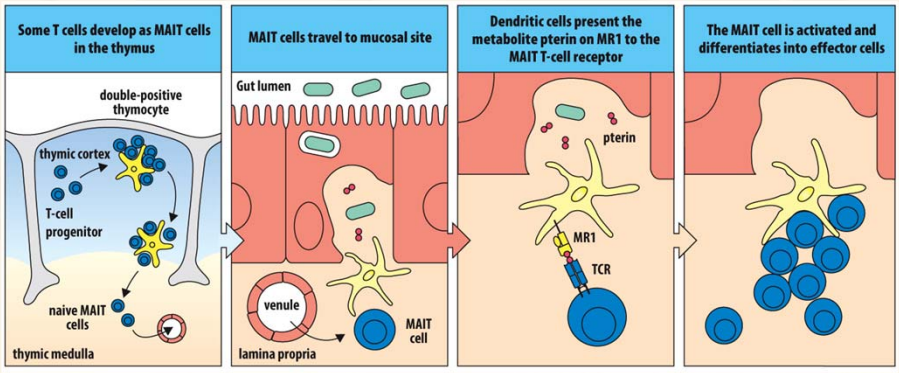

Figure 12.35 MAIT cell numbers and maturation are dependent on the microbiota. Like all other T cells, MAIT cells develop in the thymus, where they undergo positive selection on a population of double-positive thymocytes that express MR1. The naive MAIT cells leave the thymus in the blood and travel to mucosal tissue (first panel). In the mucosa, the MAIT cells interact with the resident dendritic cells (second panel). MR1 expressed on the dendritic cells has bound the pterins released by bacteria and yeast at the mucosal surface in the process of making riboflavin. The pterins are presented to the T-cell receptor of the MAIT cells (third panel). This stimulates the MAIT cells to divide and differentiate into effector T cells (fourth panel).