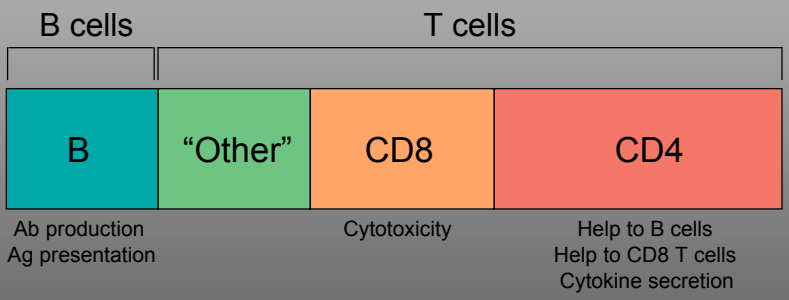
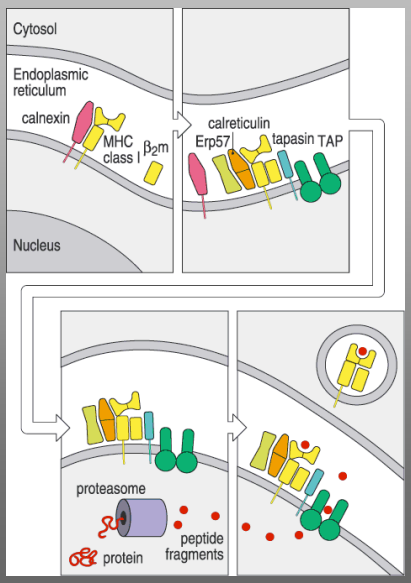
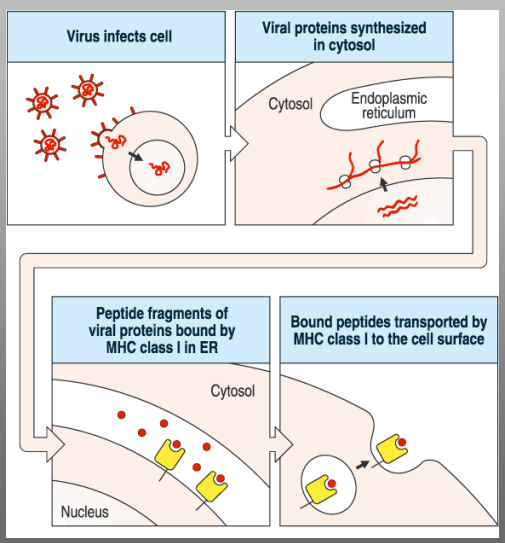
Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions



Peptide Loading on MHC Class I in the ER



What Cells Do When the Blitz is On



Antigen Presentation Pathways;
Two Old:

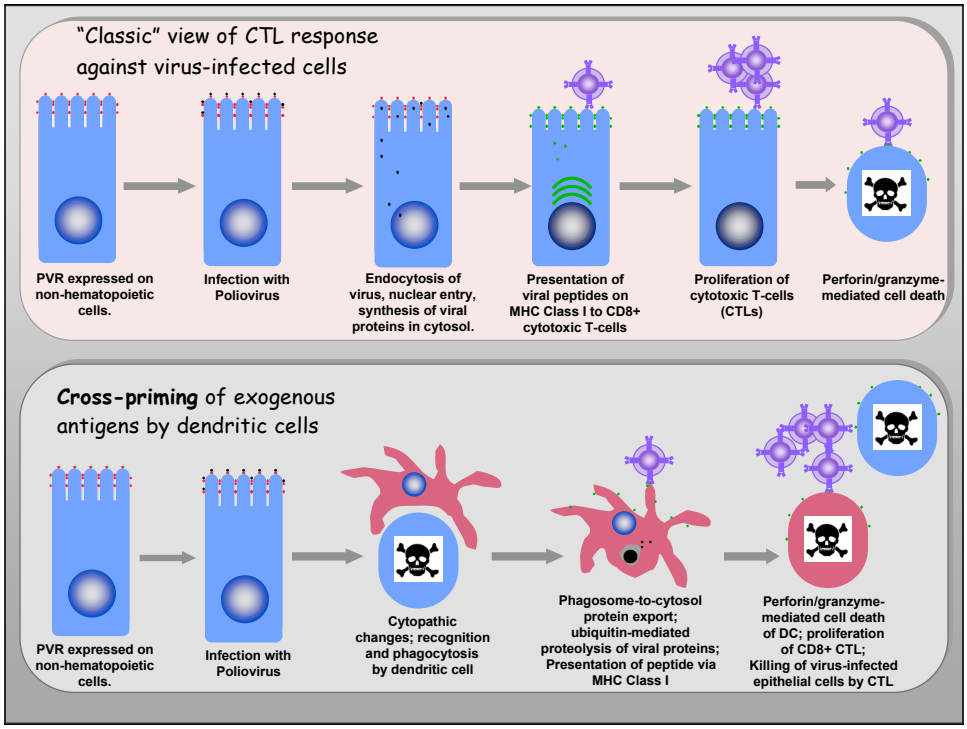
MHC Class I presentation of peptides
MHC Class II presentation of peptides

and Two New:

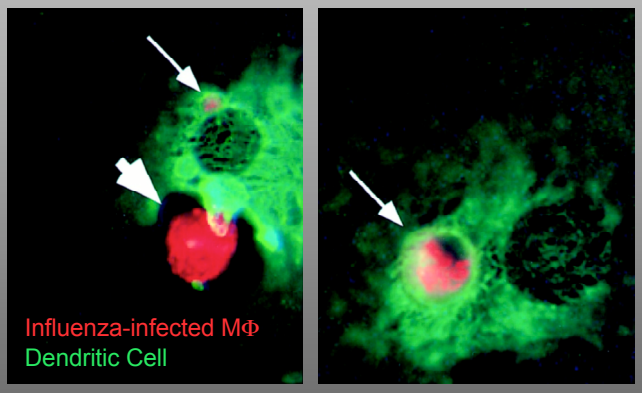
Cross-priming of exogenous peptides (MHC Class I)
CD1-mediated presentation of glycolipids

Question:

How do viruses that don't infect "professional APCs" such as dendritic cells elicit a primary immune response? After all, virally-infected cells normally don't traffic to 2° lymphoid organs



Cross-priming: A Dendritic Cell Engulfs a Viral-infected Macrophage

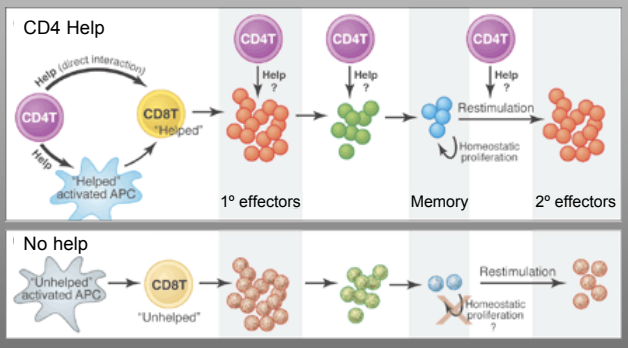


From: Albert et al., *J. Exp. Med.* 188:1359, 1998

Question:

Does development of the cytotoxic T cell response require "help" from CD4 cells (analogous to help for B cells)?

CD8 T Cells Need Help With Their Memory



Memory T-cells Don't Forget

Table 1 Estimated survival of virus-specific T-cell memory after smallpox vaccination

Vaccinations	Volunteers with CD4+ T cell memory[a] 20–30 years[b]	31–50 years	51–75 years	$t_{1/2}$ of CD4+ T cells[c]
1	100% (16/16)	89% (70/79)	52% (23/44)	10.6 (0–17)
2	83% (10/12)	78% (29/37)	57% (4/7)	8.3 (0–14.1)
3–14	82% (23/28)	91% (29/32)	ND[d]	12.4 (0–20.5)
Vaccinations	**Volunteers with CD8+ T-cell memory 20–30 years**	**31–50 years**	**51–75 years**	**$t_{1/2}$ of CD8+ T cells**
1	50% (8/16)	49% (39/79)	50% (22/44)	15.5 (0–27.1)
2	42% (5/12)	38% (14/37)	57% (4/7)	8.1 (0–16.9)
3–14	46% (13/28)	50% (16/32)	ND	9.0 (0–18.1)

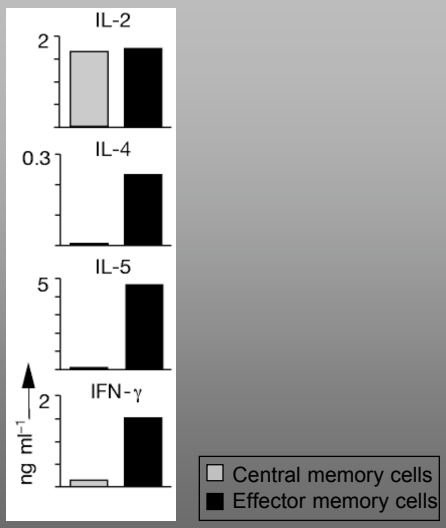
[a]Percentage of volunteers with vaccinia-specific T-cell memory is based on the proportion of immunized participants with >10 IFN-γ^+TNF-α^+ T cells per 10^6 CD4+ or CD8+ T cells, respectively. This cutoff provides 100% sensitivity at 1 month after vaccination or revaccination and 92–96% specificity, based on the vaccinia-induced IFN-γ response in T cells from unvaccinated volunteers. [b]Years after the last smallpox vaccination. [c]Estimated half-life ($t_{1/2}$) in years (and 95% confidence interval in parentheses) is based on linear regression analysis using data from Figures 1 and 2. N.D., not determined.

From: Hammarlund et al., Nature Med. 9:1131, 2003

Differences Between Selected T Cell Subsets

Phenotype	Naïve	Effector	Memory	
			Central	Effector
Migration	LN, spleen	Inflamed tissue	LN	Inflamed tissue
Cell cycle	-/+	++	+	++
Cytokine secretion	-	+++	-	+++
Peripheral LN homing (L-Selectin; CD62L)	+++	-	+++	-
Adhesion Molecules (Integrins, CD44)	+	+++	+++	+++
Chemokine Receptors (partial list)	CCR7	CCR5 CXCR4	CCR7	CCR5 CXCR4
IL-2 Receptor (CD25)	-	++	+	+/-
FasL	-	+++	-	+++

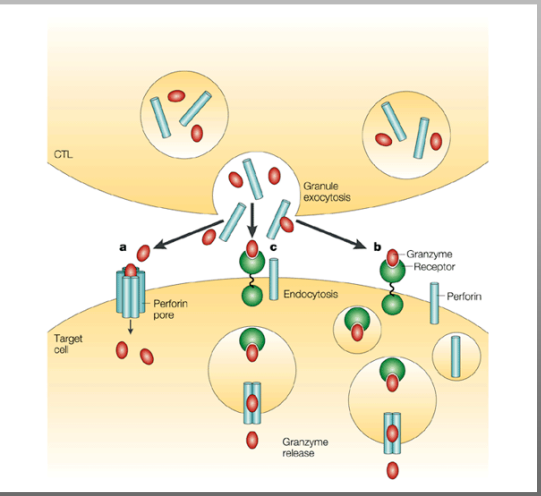
Effector Memory Cells Can Secrete Cytokines



From: Sallusto et al., *Nature* 401:708, 1999

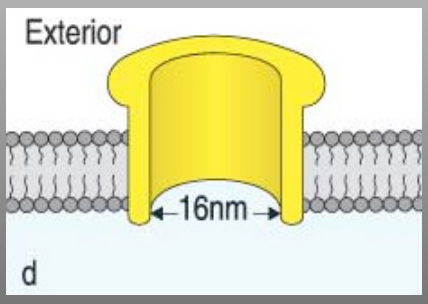
CYTOTOXIC T-LYMPHOCYTE:
A specialized white blood cell responsible for eliminating unwanted body cells (e.g. cancer) is killing a cell infected with the influenza virus

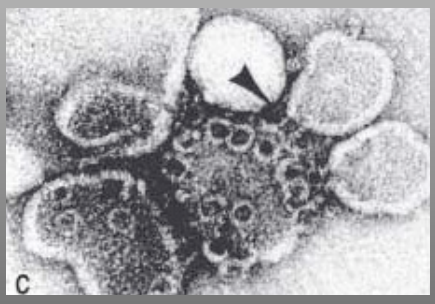
Cooperation in Killing: Granzyme and Perforin



From: Barry & Bleackely. *Nature Rev. Immunol*. 2:401, 2002

Structure of Perforin

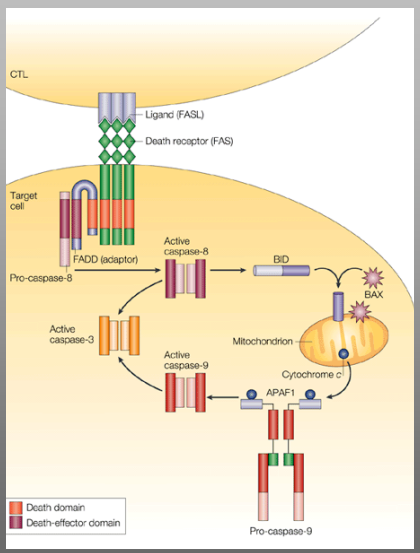




Human Diseases Involving Defective Granule Killing

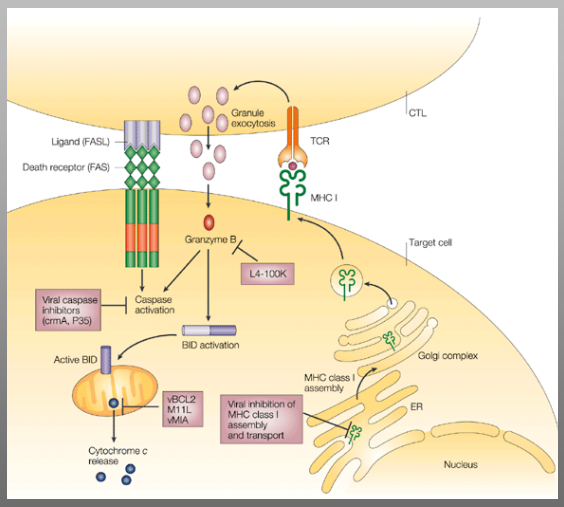
Disease	Gene	Clinical Manifestations
Chediak-Higashi Syndrome	CHS1	Lysosomal inclusions in all leukocytes Recurrent bacterial infections Decreased NK cell function Oculocutaneous albinism (melanosome defect) Bleeding (platelet storage granule defect)
Griscelli Syndrome	Rab27a	Partial albinism Hepatosplenomegaly (lymphohistiocytic infiltration) Decreased NK cell function
Hermansky-Pudlak Syndrome	HPS1	Oculocutaneous albinism (melanosome defect) Bleeding (Platelet storage granule defect) Pulmonary fibrosis (Type II cell surfactant body inclusions)
Familial Hemophagocytic Lymphohistiocytosis	Perforin (30% of cases)	Hepatosplenomegaly (accumulation of activated T-cell and macrophages) Decreased NK cell function Pancytopenia

Life (and Death) in the Fas Lane



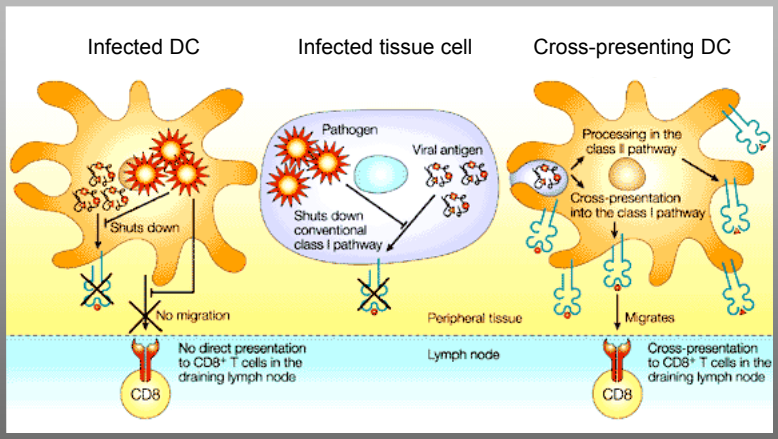
From: Barry & Bleackely. *Nature Rev. Immunol*. 2: 401, 2002

Viral Evasion of Immunity

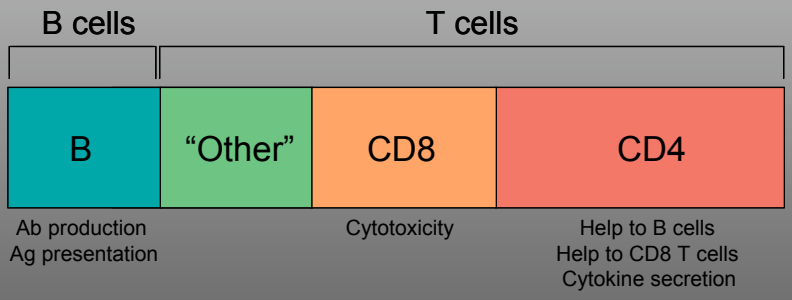


From: Barry & Bleackely. *Nature Rev. Immunol*. 2: 401, 2002

Cross-priming: DCs Fight Back

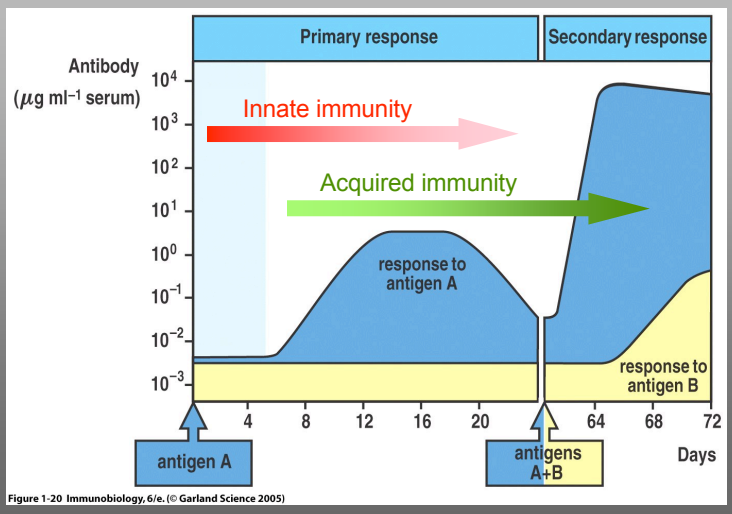


Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions



Innate-like Lymphocytes

Time Course of Innate and Adaptive Immunity



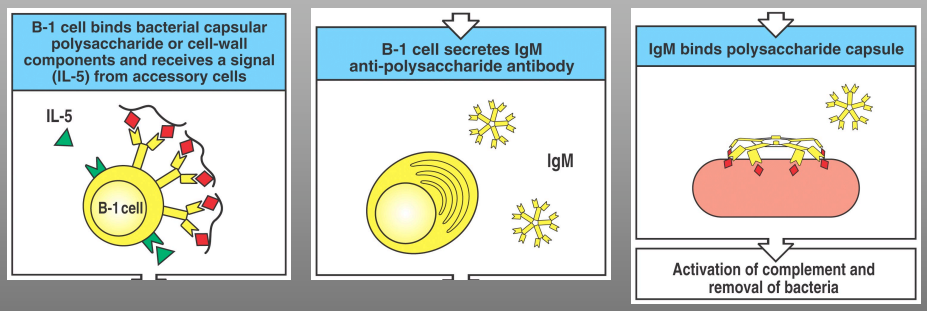
Distinctions Between Innate and Adaptive Immunity

	Innate immune system	Adaptive immune system
Receptors	Germline-encoded	Somatically engineered
Distribution	Non-clonal	Clonal
Kinetics	Rapid	Slow (requires clonal expansion)
Specificity self"	Recognizes non-self "pattern recognition"	Recognizes "altered Primary structure (TCR) Higher order structure (Immunoglobulin; BCR)
Effector Cells	All	Primarily lymphocytes; DCs, Mϕ

Innate-like B Lymphocytes

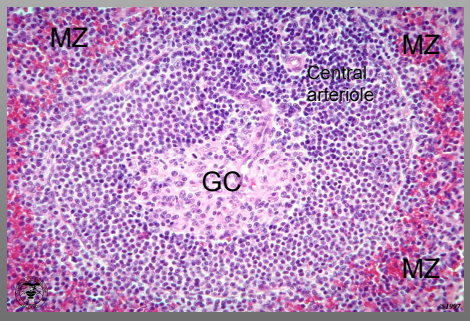
B-1 cells	Epithelial γδ cells	NK T cells	NK cells
Make natural antibody, protect against infection with *Streptococcus*	Produce cytokines rapidly	Produce cytokines rapidly	Produce cytokines rapidly
Ligands not MHC associated	Ligands are MHC class Ib associated	Ligands are lipids bound to CD1d	Ligands not MHC associated
Cannot be boosted	Cannot be boosted	Cannot be boosted	Cannot be boosted

B-1 Cells: B Prepared



Thymus-independent Antigens are Presented to Specialized B-cells

Marginal zone B cells, like B-1 cells, respond to carbohydrate antigen and secrete mainly IgM

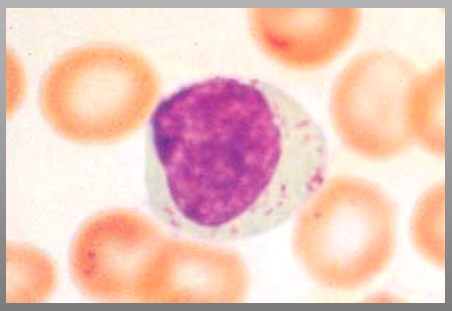


Like students who cram, after the initial encounter of Ag, they demonstrate little memory

Innate-like T Lymphocytes: NK Cells

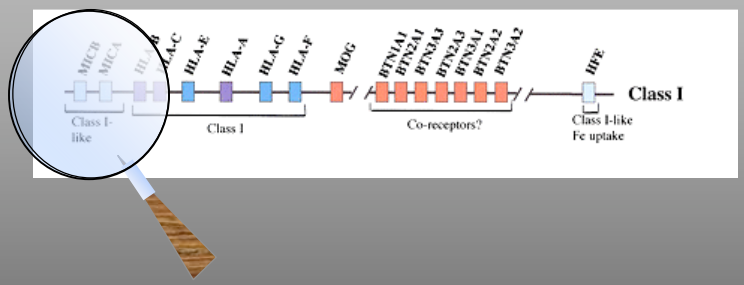
B-1 cells	Epithelial γδ cells	NK T cells	NK cells
Make natural antibody, protect against infection with *Streptococcus*	Produce cytokines rapidly	Produce cytokines rapidly	Produce cytokines rapidly
Ligands not MHC associated	Ligands are MHC class Ib associated	Ligands are lipids bound to CD1d	Ligands not MHC associated
Cannot be boosted	Cannot be boosted	Cannot be boosted	Cannot be boosted

Natural Killer Cell



How do NK Cells Recognize Their Targets?

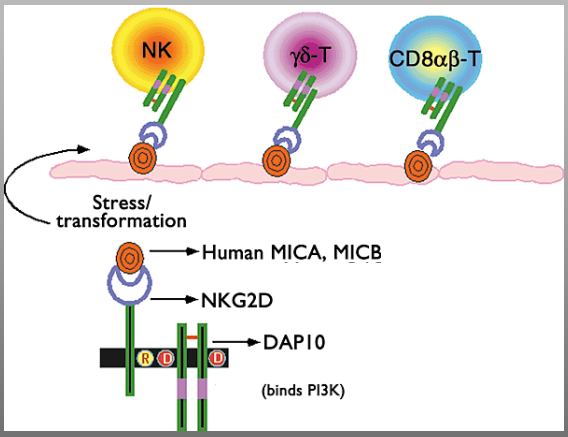
Major Genes in the MHC Class I Region



The human MHC covers ~4 Mbp of DNA on chromosome 6p21.3 and contains over 220 identified loci. It has been divided into three regions: class II (centromeric), class III, and class I (telomeric) with extended class I and class II regions on either side. This is one of the most gene-dense regions of the human genome. It encodes the most polymorphic human proteins known to date. Of the expressed loci in the MHC, roughly 40% are associated with the immune system. They include the classical class I, *HLA-A*, *-B*, and *-C*, nonclassical *HLA-E*, *-F*, and *-G*, as well as "postmodern" *MICA* and *MICB* genes (MHC class I chain-related genes). The products of classical polymorphic class I genes, HLA-A, B, and C, interact with T cell receptor (TCR) molecules as well as with the products of the *k*iller *i*mmunoglobulin-like *r*eceptor (*KIR*) genes expressed on natural killer cells and some T cells.

Trowsdale., *Immunity.* 15:363, 2001

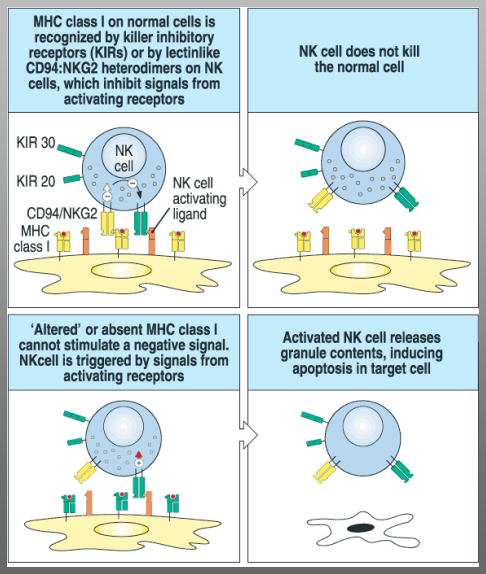
One Mechanism of Triggering NK Cell Cytotoxicity



The NKG2D-DAP10 receptor complex and its ligands. Cytotoxicity requires the expression of ligands of NKG2D (e.g., MICA, MICB) in the "stressed" target cells.

From: Lanier, *Nature Immunol.* 2:23, 2001

Why do NK Cells Fail to Recognize Healthy Cells?



Innate-like T Lymphocytes

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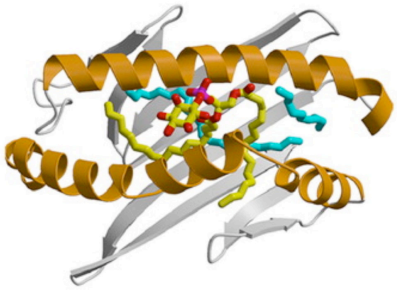
Make natural antibody, protect against infection with Streptococcus	Produce cytokines rapidly	Produce cytokines rapidly	Produce cytokines rapidly
Ligands not MHC associated	Ligands are MHC class IB associated	Ligands are lipids bound to CD1d	Ligands not MHC associated
Cannot be boosted	Cannot be boosted	Cannot be boosted	Cannot be boosted

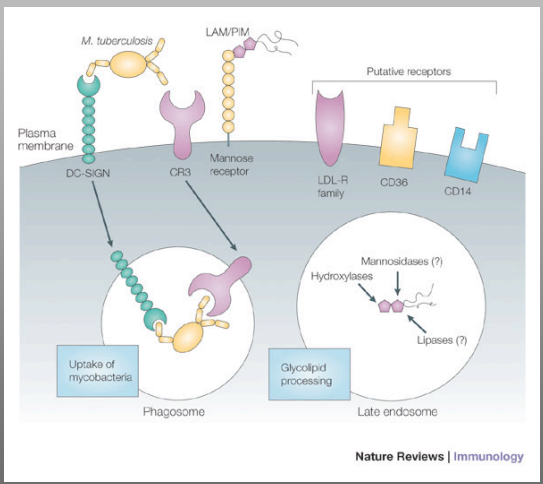
Structure of the CD1b Molecule-- Look Familiar?



CD1b with bound glycolipid antigen

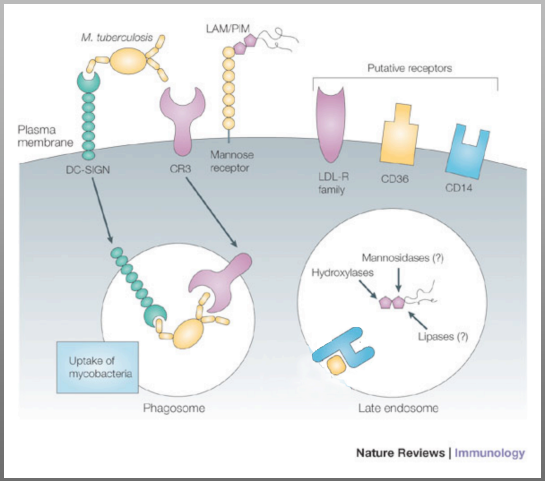
Processing of Glycolipid Antigens from *M. tuberculosis* by APCs:

I. Phagocytosis and Glycolipid Processing in Endosomes



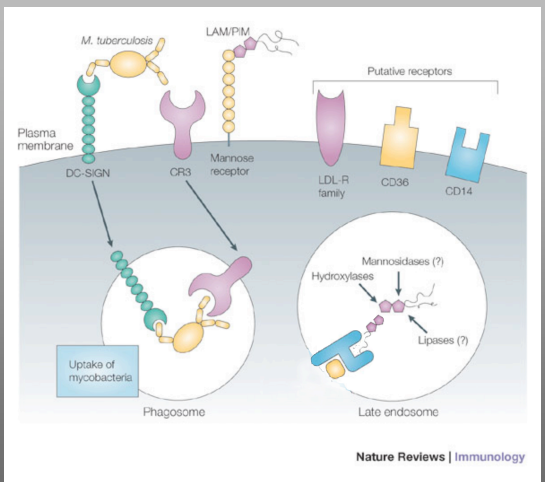
From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

II. Fusion of Endosomes with CD1d-containing Vesicles



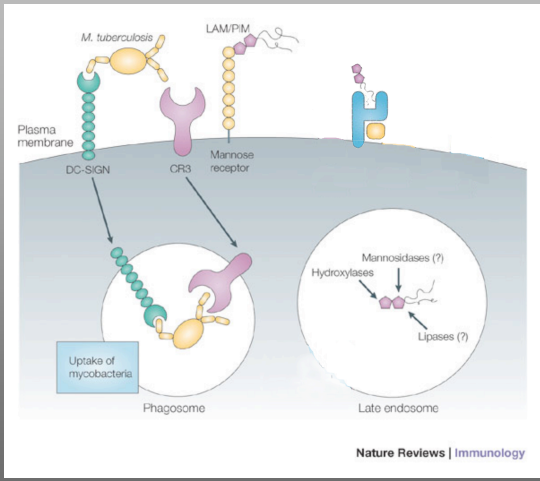
From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

III. Loading of Glycolipids onto CD1d Molecules



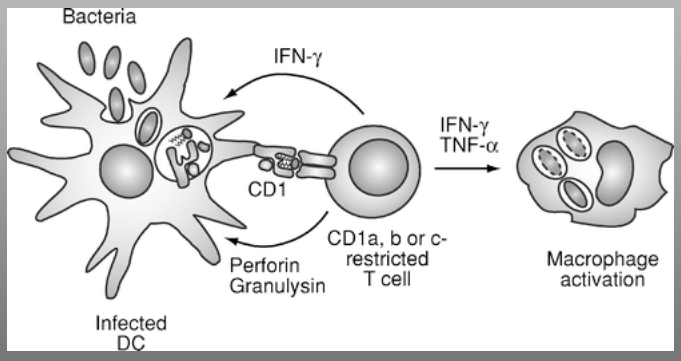
From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

VI. Trafficking of CD1d-glycolipid Complexes to the Surface of the APC



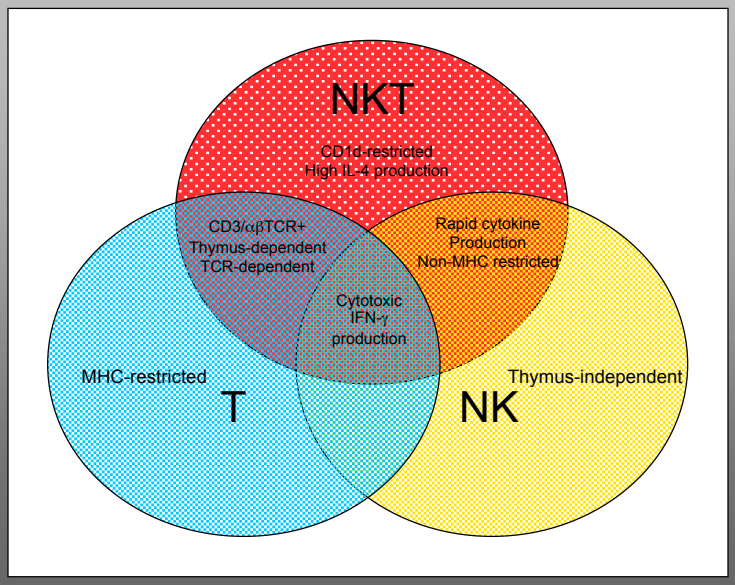
From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

The NKT Cell Recognizes Glycolipid Antigen Presented by CD1 on the APC



DCs that are infected with intracellular bacteria present foreign bacterial lipid antigens on the cell surfac bound to CD1 molecules. CD1-restricted T cells that are specific for the foreign microbial lipids are stimulated to carry out effector functions, including the secretion of cytolytic granules containing perforin and granulysin, which lyse the infected cells and have direct antimicrobial effects, respectively, and the production of IFN-γ and TNF-α, which activate the microbicidal functions of macrophages.

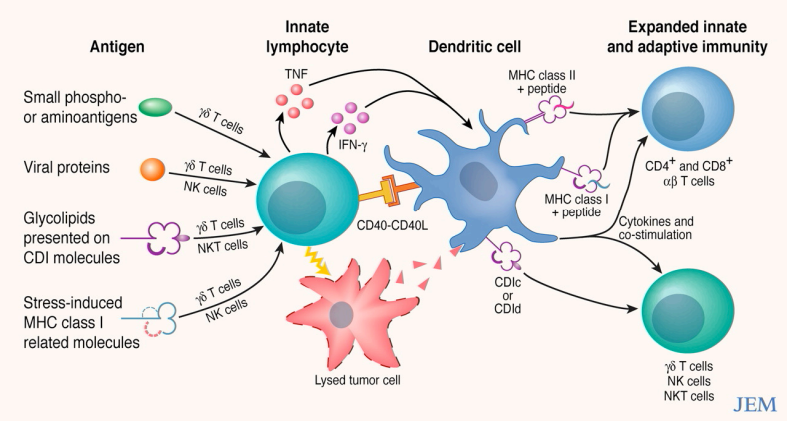
Where Do NKT Cells Fit In?



Question:

Do Lymphocytes of the Acquired Immune System Even Care about Lymphocytes of the Innate Immune System?

Innate Immune Lymphocytes Trigger Dendritic Cell Maturation



From: Munz et al., *J. Exp. Med.* 202:203, 2005

Summary

1. For cytotoxic CD8 T-cells, ligation of the TCR by MHC I/peptide + co-stimulation results in release of granzymes and perforin and/or FasL, leading to apoptosis of the target cells.

2. Viruses evade host defense, in part, by down-regulating MHC Class I. Uninfected dendritic cells circumvent this by "cross-priming": phagocytosis of virus-infected cell and presentation of "exogenous" viral antigens on MHC Class I.

3. CD8 T cells can function without CD4 help, but need CD4 help to develop into effective memory cells. CD4 memory cells live for years; central memory cells home to lymph nodes and effector memory cells home to inflamed tissue.

4. NK cells lack TCRs, but instead express both activating and inhibitory (e.g., KIRs) receptors at their surfaces. The relative expression and ligation of these receptors determines the outcome (i.e., killing or not) of the NK effector response.

5. Innate immune B-cells (e.g., B-1 cells and marginal zone B cells) recognize carbohydrate antigens, secrete IgM, and are not long-lived.

6. Innate immune T-cells (γδ T-cells, and NK T cells) recognize non-peptide antigens in non-classical MHC-like molecules. They mediate cytotoxicity, rapid cytokine secretion, and trigger maturation of DCs (and therefore initiate acquired immunity).