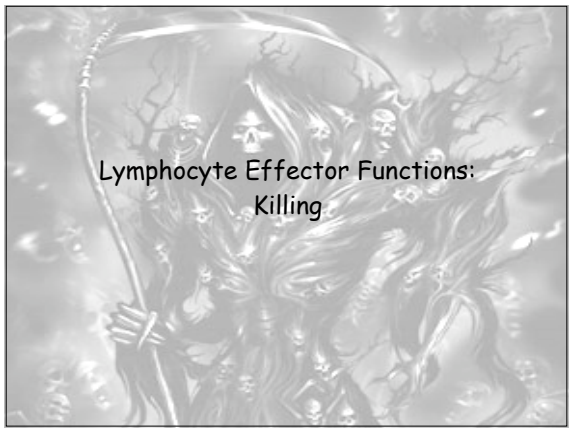
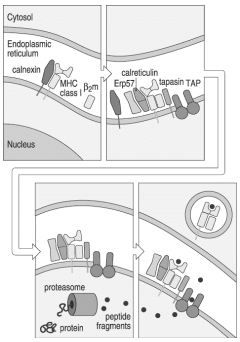


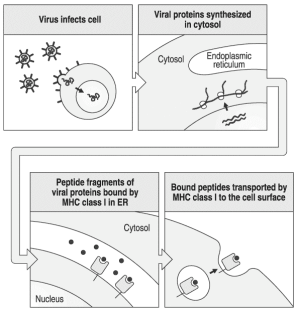

## Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions

| B cells | T cells | | |
|---|---|---|---|
| B | "Other" | CD8 | CD4 |
| Ab production<br>Ag presentation | | Cytotoxicity | Help to B cells<br>Help to CD8 T cells<br>Cytokine secretion |

## Peptide Loading on MHC Class I in the ER




## What Cells Do When the Blitz is On




Antigen Presentation Pathways;
Two Old:

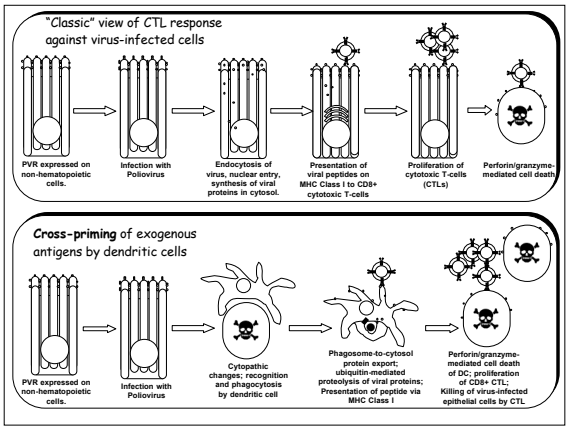
MHC Class I presentation of peptides
MHC Class II presentation of peptides

and Two New:

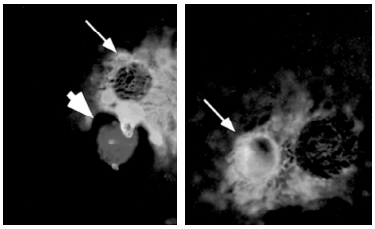
Cross-priming of exogenous peptides (MHC Class I)
CD1-mediated presentation of glycolipids

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

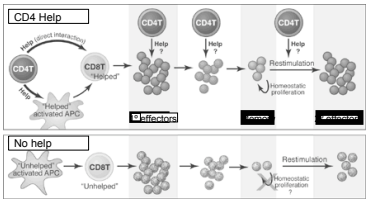


From: Albert et al., *J. Exp. Med.* 188:1359, 1998

## 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) |

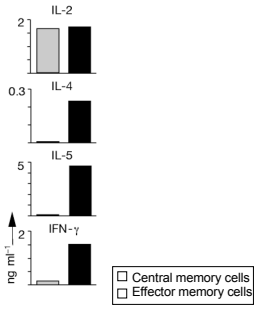
[a]Percentage of volunteers with vaccine-specific T-cell memory is based on the proportion of immunized participants with >10 IFN-$\gamma^+$TNF-$\alpha^+$ T cells per $10^6$ CD4+ or CD8+ T cells, respectively. This cutoff provides 100% sensitivity at 3 months after vaccination or revaccination and 92–96% specificity, based on the vaccine-induced IFN-$\gamma$ 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 | - | +++ | - | +++ |

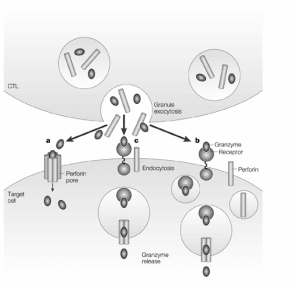
## Effector Memory Cells Can Secrete Cytokines




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

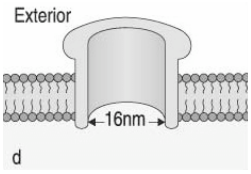
CYTOTOXIC T-LYMPHOCYTE: A specialized white blood cell responsible for eliminating unwanted body cells (e.g. cancer) is killing a cell infected with the influenza virus

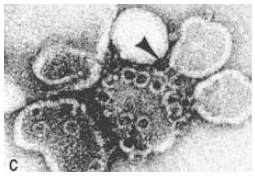
## Cooperation in Killing: Granzyme and Perforin




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

## Structure of Perforin

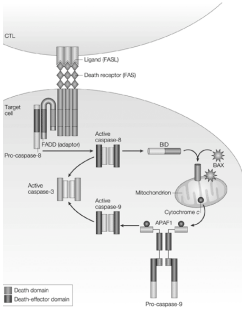



## Human Diseases Involving Defective Granule Killing

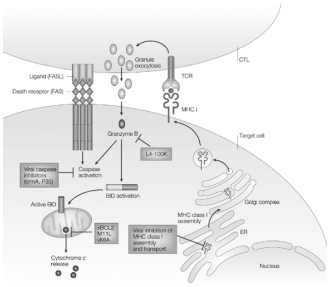
| Disease | Gene | Clinical Manifestations |
|---|---|---|
| Chediak-Higashi Syndrome | CHS1 | Lysosomal inclusions in all leukocytes<br>Recurrent bacterial infections<br>Decreased NK cell function<br>Oculocutaneous albinism (melanosome defect)<br>Bleeding (platelet storage granule defect) |
| Griscelli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

## Life (and Death) in the Fas Lane



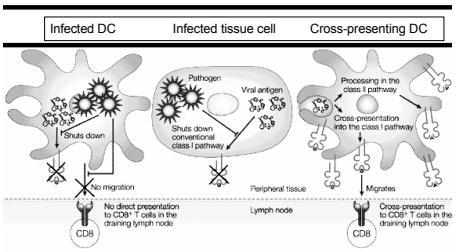

From: Barry & Bleackely. *Nature Rev. Immunol*. 2: 401, 2002

## Viral Evasion of Immunity




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

## Cross-priming: DCs Fight Back

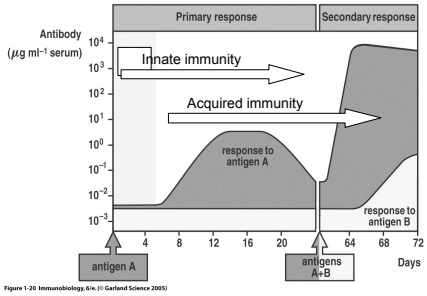



## Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions

| B cells | T cells | | |
|---|---|---|---|
| B | "Other" | CD8 | CD4 |
| Ab production<br>Ag presentation | | Cytotoxicity | Help to B cells<br>Help to CD8 T cells<br>Cytokine secretion |

## Innate-like Lymphocytes

## Time Course of Innate and Adaptive Immunity



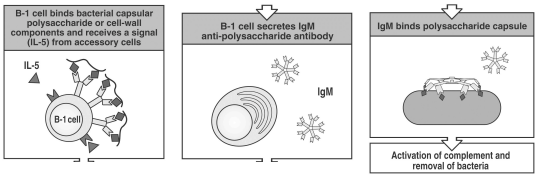

## Distinctions Between Innate and Adaptive Immunity

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

## Innate-like B Lymphocytes

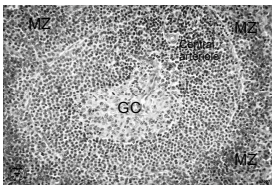
| B-1 cells | | | |
|---|---|---|---|
| Make natural antibody, protect against infection with *Streptococcus* | | | |
| Ligands not MHC associated | | | |
| Cannot be boosted | | | |

## 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

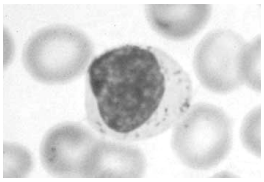



Like students who cram, after the initial encounter of Ag, they demonstrate little memory

## Innate-like T Lymphocytes: NK Cells

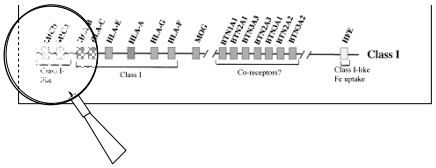
| | | | NK cells |
|---|---|---|---|
| | | | Produce cytokines rapidly |
| | | | Ligands not MHC associated |
| | | | Cannot be boosted |

## Natural Killer Cell



## How do NK Cells Recognize Their Targets?

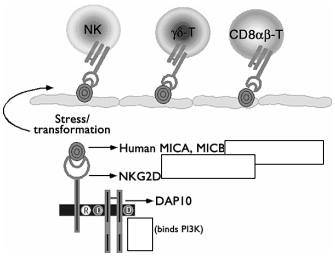
## Major Genes in the MHC Class I Region




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 *killer i*mmunoglobulin-like *r*eceptor (*KIR*) genes expressed on natural killer cells and some T cells.

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

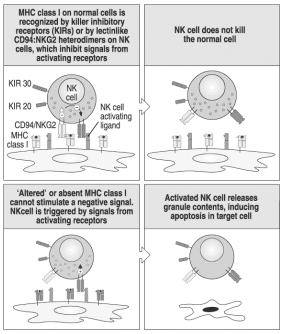
## One Mechanism of Triggering NK Cell Cytotoxicity




**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

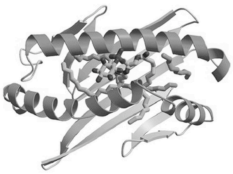
## Why do NK Cells Fail to Recognize Healthy Cells?




## Innate-like T Lymphocytes

| | Epithelial γ:δ cells | NK T cells | |
|---|---|---|---|
| | Produce cytokines rapidly | Produce cytokines rapidly | |
| | Ligands are MHC class IB associated | Ligands are lipids bound to CD1d | |
| | Cannot be boosted | Cannot be boosted | |

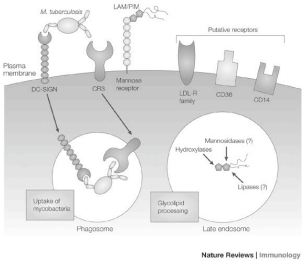
## Structure of the CD1b Molecule-- Look Familiar?



CD1b with bound glycolipid antigen

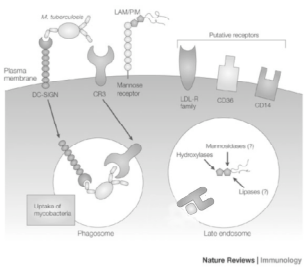
## Processing of Glycolipid Antigens from *M. tuberculosis* by APCs:

## I. Phagocytosis and Glycolipid Processing in Endosomes



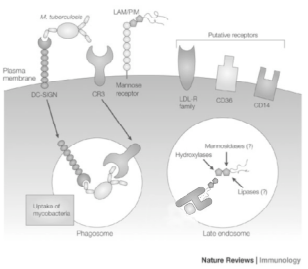

From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

## II. Fusion of Endosomes with CD1d-containing Vesicles



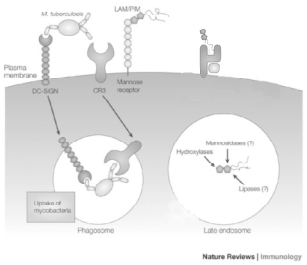

From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

## III. Loading of Glycolipids onto CD1d Molecules



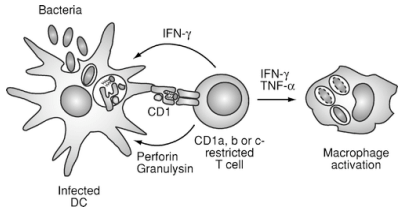

From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

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



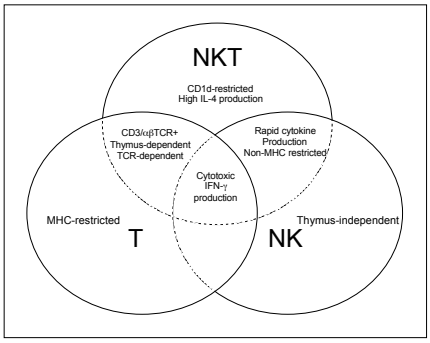

From: DeLibero and Mori, *Nature Rev. Immunol.* 5:485, 2005

## 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.

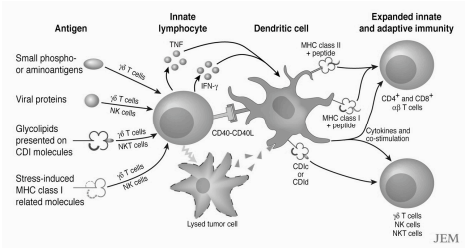
## Where Do NKT Cells Fit In?




## 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 ($\gamma\delta$ 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).