Lymphocyte Effector Functions: Killing

Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions

<table>
<thead>
<tr>
<th>B cells</th>
<th>CD8</th>
<th>CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>“Other”</td>
<td>CD8</td>
</tr>
<tr>
<td>Ab production</td>
<td>Ag presentation</td>
<td>Cytokindity</td>
</tr>
<tr>
<td>Help to B cells</td>
<td>Help to CD8 T cells</td>
<td>Cytokine secretion</td>
</tr>
</tbody>
</table>

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 don’t normally traffic to lymphoid organs.
PVR expressed on non-hematopoietic cells.

Infection with Poliovirus

Endocytosis of virus, nuclear entry, synthesis of viral proteins in cytosol.

Presentation of viral peptides on MHC Class I to CD8+ cytotoxic T-cells

Proliferation of cytotoxic T-cells

Perforin/granzyme-mediated cell death

"Classic" view of CTL response against virus-infected cells

Cross-priming of exogenous antigens by dendritic cells

Cross-priming of exogenous antigens by dendritic cells

PVR expressed on non-hematopoietic cells.

Infection with Poliovirus

Cytopathic changes; recognition and phagocytosis by dendritic cell

Phagosome-to-cytosol protein export; ubiquitin-mediated proteolysis of viral proteins; Presentation of peptide via MHC Class I

Perforin/granzyme-mediated cell death of DC; proliferation of CD8+ CTL; Killing of virus-infected epithelial cells by CTL

"Cross-priming: A Dendritic Cell Engulfs a Viral-infected Macrophages"

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

On the Job Training for CTLs

CD8 T Cells Need Help With Their Memory

Cooperation in Killing: Granzyme and Perforin

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

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Structure of Perforin

Cellular Events at the Synapse Between CTL and Target Cells

Transfer of membrane proteins at the synapse. A series of still frames from a movie showing CTLs killing a target cell. The membrane of which one frame is shown, was labeled with a fluorescent protein marker. Electron micrographs showing roughly equivalent stages of synapse formation. Granules polarize towards the immunological synapse as the CTL engages its target (a–c); as the CTL disengages, the granules withdraw from the synapse, where membrane from the target has accumulated. As the CTL detaches, target membrane is ripped off the dying target (d), and the CTL can engage a new target (color panel of e).


Human Diseases Involving Defective Granule Killing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chediak-Higashi Syndrome</td>
<td>CHS1</td>
<td>Lysosomal inclusions in all leukocytes, Recurrent bacterial infections, Oculocutaneous albinism (melanosome defect), Bleeding (platelet storage granule defect)</td>
</tr>
<tr>
<td>Griscelli Syndrome</td>
<td>Rab27a</td>
<td>Partial albinism, Hepatospleno-megaly (lymphohistiocytic infiltration), Decreased NK cell function</td>
</tr>
<tr>
<td>Hermansky-Pudlak Syndrome</td>
<td>HPS1</td>
<td>Oculocutaneous albinism (melanosome defect), Bleeding (platelet storage granule defect), Pulmonary fibrosis (Type II cell surfactant body inclusions)</td>
</tr>
<tr>
<td>Familial Hemophagocytic Lymphohistiocytosis</td>
<td>Perforin</td>
<td>(33% of cases) Hepatosplenomegaly (accumulation of activated T-cell and macrophages), Decreased NK cell function, Pancytopenia</td>
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Life (and Death) in the Fas Lane

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Viral Evasion of Immunity

Cross-priming: DCs Fight Back


Innate-like Lymphocytes

<table>
<thead>
<tr>
<th>B cells</th>
<th>T cells</th>
</tr>
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<tbody>
<tr>
<td>B1, NK, NKT, γδ</td>
<td></td>
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Time Course of the Primary Immune Response

Innate immunity

Acquired immunity

Distinctions Between Innate and Adaptive Immunity

<table>
<thead>
<tr>
<th>Innate immune system</th>
<th>Adaptive immune system</th>
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<tbody>
<tr>
<td>Receptors</td>
<td>Germline-encoded</td>
</tr>
<tr>
<td>Distribution</td>
<td>Non-clonal</td>
</tr>
<tr>
<td>Kinetics</td>
<td>Rapid</td>
</tr>
<tr>
<td>Specificity</td>
<td>Recognizes non-self “pattern recognition”</td>
</tr>
<tr>
<td>Effector Cells</td>
<td>All</td>
</tr>
</tbody>
</table>

B-1 Cells: B Prepared

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

Thymus-independent Antigens are Presented to Specialized B-cells

Like students who cram, after the initial encounter of Ag, they demonstrate little memory
Innate-like T Lymphocytes: NK Cells

Natural Killer Cell

How do NK Cells Recognize Their Targets?

Major Genes in the MHC Class I Region

One Mechanism of Triggering NK Cell Cytotoxicity

Why do NK Cells Fail to Recognize Healthy Cells?

The NKG2D-DAP10 receptor complex and its ligands. A representation of NKG2D-DAP10 receptor expression and the interaction of NKG2D-DAP10 with its ligands. Cytotoxicity requires the expression of ligands of NKG2D (e.g., MICA, MICB) on the target cells.

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The Balance of Activating and Inhibitory Signals Determines the Outcome of the NK Effector Response

X-linked Lymphoproliferative Disease

Rare (prevalence of 1/1,000,000)
- X-linked
- Defect in cytotoxicity
- Uncontrolled T-cell activation from excessive cytokine secretion, especially in response to EBV infection
- Defect apparent in NK cells and CTL
- Patients are treated with bone marrow transplantations of hematopoietic stem cells

Molecular Defect of X-linked Lymphoproliferative Disease

- Syk: a protein tyrosine kinase
- PI 3-kinase: a phosphoinositide kinase
- SHP-2: A protein tyrosine phosphatase

Innate-like T Lymphocytes

- Epithelial p53 cells
  - NK T cells
  - Produce cytokines rapidly
  - Ligands are MHC class I associated
  - Cannot be boosted

Structure of the CD1b Molecule--Look Familiar?

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

CD1b

DCs that are infected with intracellular bacteria present foreign bacterial lipid antigens on the cell surface 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 lyses 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?

NKT
- MHC-restricted Thymus-independent
- Rapid cytokine Production
- Non-MHC restricted
- CD1d-restricted
- High IL-4 production

CD3/αβ TCR+
- Thymus-dependent
- TCR-dependent
- Cytotoxic
- IFN-γ production

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. The innate immune system has a rapid onset and recognizes molecular patterns in a non-clonal fashion.
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.

Summary
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