T cells IV: Cytotoxicity and Cell Death

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

Memory T-cells Don’t Forget

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration</td>
<td>LN, spleen</td>
</tr>
<tr>
<td>Cell cycle</td>
<td>-</td>
</tr>
<tr>
<td>Cytokine secretion</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral LN homing</td>
<td>-</td>
</tr>
<tr>
<td>Adhesion Molecules (integrins, CD44)</td>
<td>-</td>
</tr>
<tr>
<td>Chemokine Receptors (partial list)</td>
<td>CCR7</td>
</tr>
<tr>
<td>TLR Receptors (partial list)</td>
<td>-</td>
</tr>
</tbody>
</table>

Phenotypic Differences Between Selected T Cell Subsets

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<thead>
<tr>
<th>Phenotype</th>
<th>Naive</th>
<th>Effector</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration</td>
<td>LN, spleen</td>
<td>Infused tissue</td>
<td>LN, Infused tissue</td>
</tr>
<tr>
<td>Cell cycle</td>
<td>-/+</td>
<td>++</td>
<td>-/++</td>
</tr>
<tr>
<td>Cytokine secretion</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Peripheral LN homing</td>
<td>+++</td>
<td>-/+++</td>
<td>+++</td>
</tr>
<tr>
<td>Adhesion Molecules</td>
<td>CCR7, CXCR4, CCR5</td>
<td>CCR7, CXCR4, CCR7</td>
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</tr>
<tr>
<td>IL-2 Receptor (CD25)</td>
<td>-/+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>T-cell</td>
<td>-/++</td>
<td>+++</td>
<td>-/+++</td>
</tr>
</tbody>
</table>

Effector Memory Cells Can Secrete Cytokines

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

Cooperation in Killing: Granzyme and Perforin


Structure of Perforin

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, Decreased NK cell function, Oculocutaneous albinism (melanosome defect)</td>
</tr>
<tr>
<td>Gitelman Syndrome</td>
<td>Rab27a</td>
<td>Partial albinism, Hepatoplenomegaly, 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 (20% of cases)</td>
<td>Hepatoplenomegaly (accumulation of activated T-cell and macrophages), Decreased NK cell function, Panhypoplasia</td>
</tr>
</tbody>
</table>
Life (and Death) in the Fas Lane


The TNF Superfamily and Selected Immune Functions

Receptor on T cell | Ligand | Immune Function | Disease Associations
--- | --- | --- | ---
Fas | Fas-L | Apoptosis | RA, IBD, peripheral ALPS
RANK | RANKL | Bone resorption (osteoclasts) | RA, IBD, psoriasis
LTα/β | TNF-α, TNF-β | Inflammation | RA, IBD
CD40 | CD40L | Co-stimulation of memory CD8+ T cells | viral
4-1BB | 4-1BBlig | Co-stimulation of activated CD4+ T cells | GVHD, RA, IBD
OX40 | OX40L | Co-stimulation of activated CD4+ T cells | RA, IBD
BCMA, TACI, BAFFR | APRIL, BAFF | ALPS, RA, IBD, psoriasis

The TNF Superfamily and Selected Immune Functions

Viral Evasion of Immunity


Cross-priming: DCs Fight Back


Major Lymphocyte Subpopulations in Peripheral Blood and Selected Effector Functions

<table>
<thead>
<tr>
<th>B cells</th>
<th>T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>&quot;Other&quot;</td>
</tr>
<tr>
<td>Ag production</td>
<td>Cytokinesis</td>
</tr>
</tbody>
</table>

RA = Rheumatoid arthritis
IBD = Inflammatory bowel disease
ALPS = Autoimmune lymphoproliferative syndrome
XLA = X-linked agammaglobulinemia
GVHD = Graft-vs-host disease
CVID = Common variable immunodeficiency
B cells

T cells

B1 NKT, γδ

Innate-like Lymphocytes

Innate-like B Lymphocytes

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

After the initial encounter of Ag, they demonstrate little memory (like trying to cram this course).

Innate-like T Lymphocytes:

NK Cells

Natural Killer Cell

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

After the initial encounter of Ag, they demonstrate little memory (like trying to cram this course).
How do NK Cells Recognize Their Targets?

The human MHC covers ~4 Mbp of DNA on chromosome 6p and contains over 220 identified loci that have been divided into two major regions: class I (telomeric) and class II (centromeric) with extended class I and class II regions on either side. This is one of the gene-densest regions of the human genome. It encodes the most polymorphic human proteins known to date. Of the expressed genes in the MHC, roughly 10% 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 the T cell receptor (TCR) molecules as well as with the products of the killer immunoglobulin-like receptor (KIR) genes expressed on natural killer cells and some T cells.

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.

Why do NK Cells Fail to Recognize Healthy Cells?

Innate-like T Lymphocytes

- Produce cytokines rapidly
- Tumoricidal activity
- Ligands are MHC class II restricted
- Cannot be localized

Innate-like T Lymphocytes

- Produce cytokines rapidly
- Tumoricidal activity
- Ligands are not bound by CD8
Structure of the CD1b Molecule--Look Familiar?

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

I. Phagocytosis and Glycolipid Processing in Endosomes

II. Fusion of Endosomes with CD1d-containing Vesicles

III. Loading of Glycolipids onto CD1d Molecules

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


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. 202:210, 2005

Summary

1. For cytotoxic CD8 T-cells, ligation of the TCR by MHC I/peptide + co-stimulation results in release of granzymes and perform/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 on 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).