MICR2209

Adaptive immune responses: T cell-mediated immunity

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Synopsis: In this lecture we will discuss the T-cell mediated immune response, how it is activated, and the major effector functions which are involved.

Outcomes: You should be able to describe the major cell types of the cell mediated immune response; how and where T cells mature; how they are activated; the different CD4+ T cell subsets and their effector functions; cross-presentation.
Figure 10-1 Immunobiology, 7ed. (© Garland Science 2008)
The adaptive cell-mediated immune response is initiated by dendritic cells which have sampled antigen in host tissues.
T cell development in the thymus

T cells develop from progenitors that are derived from hematopoietic stem cells in the bone marrow and migrate through blood to the thymus, where they mature.

T cell development parallels B cell development in many ways, including rearrangement of antigen-receptor genes, sequential testing for successful gene rearrangement, and the eventual formation of a complete heterodimeric antigen receptor.
Selection in thymus

αβ TCR that are compatible with self-MHC molecules transmit a survival signal on interacting with thymic epithelium, leading to positive selection of the T cells that bear them.

Self-reactive TCR transmit a signal that leads to cell death, in a process of negative selection. Tissue specific antigens, for example pancreatic insulin, would not be expected to be expressed in the thymus – the autoimmune regulator gene AIRE acts to present self antigens in stromal cells in thymic medulla for recognition by T cells.
T cells are activated in peripheral lymphoid organs

T cells that survive selection mature and leave the thymus to circulate in the blood. They repeatedly leave the blood to migrate through the peripheral lymphoid organs, where they may encounter their specific antigen and become activated.
Activated T cells become effector cells

Mature T cells that encounter their specific (cognate) antigen are activated.

Activation leads to clonal expansion and differentiation into effector T cells, which are attracted to sites of infection where they can kill infected cells (CD8+ T cells) or activate macrophages (CD4+ T cells).

Other T cells move into B cell-rich areas of LT where they help to provide an antibody response (not shown)
T cell homeostasis

- T cells which have matured within the thymus for about 1 week emigrate to the periphery
- Relatively small numbers are exported (about 1-2x10^6/day in the mouse)
- In the absence of infection this pool of naïve T cells is kept at a roughly constant size and composed of diverse TCR by a regulatory process called homeostasis, which involves cytokines - including IL-7 - and signals received by TCR in response to contact with self-peptide/MHC, for example on DC in T cell-rich zones of LT
Activation of naïve T cells requires 3 kinds of signals, delivered by antigen presenting cells

1. TCR and foreign peptide: MHCII complex is indicator for activation

2. Co-stimulatory signal eg. CD28 on naïve T cell and B7 on APC determines survival for cells which have been activated by Signal 1

3. Cytokines and other mediators are released by APC and determine differentiation pathway and therefore T cell effector function

CD4+ T cells are shown in this example
Antigen presenting cells are distributed differentially in lymph node

Dendritic cells are found throughout the LN cortex, in the T cell-rich areas

Macrophages are distributed throughout

B cells are found mainly in the follicles

The three types of APC are adapted to present different types of pathogen or pathogen products, but mature DC are by far the strongest activators of naïve T cells
T cell proliferative response is regulated by CTLA-4

Naïve T cells express CD28, which delivers a costimulatory signal on binding B7 expressed by APC, driving expansion of T cells.

Once activated, T cells express increased levels of CTLA-4, which has a higher affinity for B7 than CD28.

CTLA-4 thus binds most or all of the available B7, serving to regulate the proliferative phase of the response.
Antigen recognition in absence of co-stimulation leads to functional inactivation of peripheral T cells

Not all T cells capable of recognizing self antigen are deleted in the thymus. Effective activation of naïve T cells requires both TCR/pMHC recognition and CD28 costimulation by B7 expressed by activated DC. In the absence of CD28 ligation a naïve T cell activated by Signal 1 alone enters a state of anergy: self antigens induce tolerance in the peripheral T cell population.

Anergic T cells cannot be activated even if specific antigen is subsequently presented along with correct costimulatory signals: clonal deletion.
IL-2 is required for T cell proliferation

Activated T cells secrete and respond to IL-2

Activation of naïve T cells in the presence of costimulation with CD28 induces expression and secretion of IL-2, and the expression of high-affinity IL-2 receptors. IL-2 binds to the IL-2R to promote T cell growth and proliferation.
# T cells in humoral and cell-mediated immune responses

<table>
<thead>
<tr>
<th>Types of effector T cell</th>
<th>CD8 cytotoxic T cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;1 cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;2 cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;17 cells</th>
<th>CD4 regulatory T cells (various types)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL</td>
<td>Kill virus-infected cells</td>
<td>Activate infected macrophages Provide help to B cells for antibody production</td>
<td>Provide help to B cells for antibody production, especially switching to IgE</td>
<td>Enhance neutrophil response</td>
<td>Suppress T-cell responses</td>
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<tr>
<td>Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria</td>
<td>Microbes that persist in macrophage vesicles (e.g. mycobacteria, Listeria, Leishmania donovani, Pneumocystis carinii) Extracellular bacteria</td>
<td>Helminth parasites</td>
<td>Extracellular bacteria (e.g. Salmonella enterica)</td>
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Figure 8-1 Immunobiology, 7ed. (© Garland Science 2008)
CD4+ T\textsubscript{H}17 cells

Naïve CD4+ T cells respond to specific peptide:MHCI\textsubscript{I} (and co-stimulation) by making IL-2 and proliferating.

APC, mostly DC, generate various cytokines or express molecules that act as Signal 3 to induce development of CD4+ into effector cells.

Exact form of Signal 3 depends on APC and environment.

Early in infection, IL-6 produced by activated DC induces CD4+ T cells to differentiate into T\textsubscript{H}17 cells, which are important in neutrophil recruitment and anti-microbial defense.
Later in infection, DC and other APC produce different cytokines to act as Signal 3: IFNγ and IL-12. These molecules promote CD4+ T cell differentiation into $T_H^1$ cells which produce Interferon-$\gamma$ (IFN$\gamma$) upon recognition of their target cell (thus reinforcing the signal for differentiation into more $T_H^1$ cells). $T_H^1$ cells promote macrophage activation which clears intracellular infection, and also provides T cell help for production of protective antibodies. Also upregulates MHCI and MHCII expression.
CD4+ \( T_h \)2 cells

TH2 cells produce the cytokine IL-4, which stimulates production of IgE, and IL-5, which activates eosinophils.

IgE participates in activation of mast cells, and coats helminths, and eosinophils destroy the helminths.

The antibodies produced by TH2 activation may neutralize microbes and toxins but do not activate complement.
Effector T cells migrate to sites of infection by using receptors that bind to ligands that are induced on endothelium by cytokines produced during innate immune responses to microbes. T cells leave the circulation and enter peripheral tissues. T cells which recognize their cognate antigen carry out effector functions, whereas those T cells that do not see antigen return to circulation via lymphatic vessels.
Effector T cells can respond to their target cells without costimulation.
The balance between $T_H1$ and $T_H2$ cell activation determines the outcome of intracellular infections.

### Infection Response Outcome

<table>
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<tr>
<th>Infection</th>
<th>Response</th>
<th>Outcome</th>
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<tbody>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>Some patients: $T_H1$ Some patients: Defective $T_H1$ or dominant $T_H2$</td>
<td>$\Rightarrow$ Tuberculoid leprosy Lepromatous leprosy (high bacterial count)</td>
</tr>
</tbody>
</table>
Some pathogens can resist the effects of macrophage activation

Granulomas form when an intracellular pathogen such as mycobacteria cannot be totally eliminated.

A characteristic localized inflammatory response occurs: a central core of infected macrophages (which may become necrotic) surrounded by T cells (many of which are CD4+).

Granulomas also form in the lungs and elsewhere in sarcoidosis, which may be caused by inapparent mycobacterial infection
Killing by CD8+ cytotoxic T lymphocytes

CTLs recognize MHCI-associated peptides (peptide antigens derived from intracellular microbes) and form tight adhesions ("conjugates") with these target cells.

The CTL are activated to release granules such as granzyme, which are taken into the target cell and where they induce apoptosis (programmed cell death)
Cytotoxic T cells kill target cells bearing specific antigen while sparing neighbouring uninfected cells.

Cytotoxic effector proteins that trigger apoptosis are contained in the granules of CD8+ CTL.

<table>
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<tr>
<th>Protein in granules of cytotoxic T cells</th>
<th>Actions on target cells</th>
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<tr>
<td>Perforin</td>
<td>Aids in delivering contents of granules into the cytoplasm of target cell</td>
</tr>
<tr>
<td>Granzymes</td>
<td>Serine proteases, which activate apoptosis once in the cytoplasm of the target cell</td>
</tr>
<tr>
<td>Granulysin</td>
<td>Has antimicrobial actions and can induce apoptosis</td>
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</table>
Viral infection results in presentation of viral peptide antigens on cell surface, in context of MHC1
Naïve CD8+ T cells are activated by cross-presentation

Dendritic cells provide the costimulatory molecules needed to activate naive CD8+ T cells. DC internalize infected cells and transfer the microbial peptide antigen into the MHC1 antigen processing pathway; naïve CD8+ T cells can now receive Signals 1 & 2 and undergo activation.
Summary: The phases of an adaptive immune response

1. Antigen recognition
2. Lymphocyte activation
3. Antigen elimination
4. Contraction (homeostasis)
5. Memory

- Clonal expansion
- Differentiation
- Humoral immunity
- Cell-mediated immunity
- Elimination of antigens
- Apoptosis

Antigen-presenting cell → Naive T lymphocyte → Effector T lymphocyte → Antibody-producing cell

Days after antigen exposure:
- 0
- 7
- 14