T Cell Effector Mechanisms I: B cell Help & DTH

Ned Braunstein, MD

The Major T Cell Subsets

CD4+ T cells
- Interacts with MHC class II expressing cells (B cells, macrophages)
- Induce (help) B cells to synthesize antibody
- Induce and activate macrophages
- Secretes lymphokines

CD8+ T cells
- Interacts with MHC class I expressing cells (all nucleated cells)
- Kill MHC class I expressing target cells
- Suppress immune responses
- Secretes lymphokines
Observations

- T cells responses to foreign proteins are readily made in setting of infection
  - Immunization to foreign protein provided outside the setting of infection requires adjuvant
- T cells capable of responding to self MHC + plus peptide can be readily identified in healthy individuals
  - Autoimmune disease is rare

Implications/Overview

- T cell activation is highly regulated and involves both antigen plus context
  - APC
    - MHC molecule
      - antigen processing & presentation
    - Other cell surface molecules
      - accessory molecules and co-stimulators
  - Cytokines (and chemokines)
Molecular Interactions of Helper T Cells and APC/B Cells

CD4+ T Cell

APC/ B cell

T cell activation

Signal 1 - MHC + peptide

Signal 2 - Co-stimulation
Naïve T cells are activated by DCs presenting antigen in LNs where they mature into effector cells

Antigens are captured by DCs in peripheral tissues and processed to form MHC-peptide complexes. As a consequence of antigen deposition and inflammation, DCs begin to mature, expressing molecules that will lead to binding and stimulation of T cells in the T-cell areas of lymphoid tissues. If the antigen has also been bound by B cells, then both B and T cells can cluster with DCs. After activation, B blasts move to the lining of the intestine, the bone marrow, and other parts of the lymphoid tissue with some becoming antibody-secreting plasma cells. T blasts leave the blood at the original site of antigen deposition, recognizing changes in the inflamed blood vessels and responding vigorously to cells that are presenting antigen. This limits the T-cell response to the site of microbial infection. Banchereau, J. and Steinman, R. Nature 392, 245 - 252 (1998)
Primed effector T cells can be restimulated in tissue by antigen + MHC without requiring costimulation.
IKK: I-κB kinase
Lck, lyn, ZAP-70: Protein tyrosine kinases
Ras: Low MW GTPase
CD45: A tyrosine phosphatase

IKK: I-κB kinase
Lck, lyn, ZAP-70: Protein tyrosine kinases
Ras: Low MW GTPase
CD45: A tyrosine phosphatase
Calcineurin: A Ca\(^{2+}\)/calmodulin-activated protein phosphatase that dephosphorylates the transcription factor NF-AT, triggering its nuclear translocation, where it cooperates with other transcription factors (e.g., fos/jun) to trigger transcription (e.g., of IL-2 and its receptor)

The T cell activation cycle

- **Minutes**
  - Antigen recognition
  - Immediate events

- **Hours**
  - Cytokine production and autocrine stimulation
  - IL-2 etc.

- **Days**
  - Effector functions:
    - Help
    - DTH
    - Killing (CTL)
    - Regulation
Naïve CD4+ T cells differentiate into Th1 and Th2 subsets

Resting CD4+ cell

Activated CD4+ cell

IL-2
IFN-γ
IL-12
IFN-γ
IL-4, IL-13
Th1 Cells

IL-2
IFN-γ
IL-4
IL-10
IL-4
IL-5
IL-6
IL-10
Th2 Cells

Functions of Th subsets

Functions of Th1 subsets

• Activate macrophages/dendritic cells
  augment antigen presentation
• induce delayed type hypersensitivity
  (DTH) responses important in
  eradicating intracellular pathogens
  (TB, leprosy, listeria)
• mediate Th1 diseases (ie; rheumatoid
  arthritis, multiple sclerosis and type I
  diabetes)

Functions of Th2 subsets

• Help B cells and induce humoral
  immunity
• mediate allergic and immediate
  hypersensitivity responses
• involved in antibody mediated immune
  diseases like SLE and ITP
Major Functions of T Lymphocytes

1. Induction and Activation of B cells (Help) - required for most antibody responses

2. Delayed Type Hypersensitivity (DTH) - important in elimination of intracellular pathogens (virus, fungi and mycobacteria)

3. Cell mediated Cytotoxicity (Killer function) - important in the immune response to virus infected cells and cancer cells

4. Suppressor Cell Function - regulates the cell mediated and antibody responses

B Cell Help - Part I
B cells receive Signal 1 from Antigen and then Process and Present

Antigen binds specifically to Smlg, is internalized into vesicles and cleaved into peptides which displace and bind to MHC class II molecules. The peptide/MHC complex is then transported to the surface membrane.
B Cell Help - Part II
Antigen Presentation and Initial Activation of CD4 T cell

B Cell Help - Part III
B Cells Receive Signal 2 From T Cells via CD40

- Triggering of B cell proliferation
- Rescue from apoptosis
- Induction of Ig isotype class switching
- Up-regulation of CD80 and CD86
- Germinal center formation
- Up-regulation of CD23
- Downregulation of CD40L expression
B Cell Help - Part IV
Activated B cells Express CD80 and Deliver Signal 2 to T cell

Activated B cells Express CD80 and Deliver Signal 2 to T cell

Activated B cell

- BCR (SmIg)
- MHC class II
- CD40
- CD32
- CD23
- CD40L
- CD80
- CD86

Activated Effector T cell

- TCR
- CD4
- CD28
- CD80
- CD86

Activated Effector T cell

- IL-2R
- CD23

Activated B cell

- SmIg

Activated Effector T cell

- TCR
- CD4

Activated Effector T cell

Lymphokines
- IL-2, IL-4, IL-5, IL-6, IFN-γ, TGF-β

Plasma Cell

- IgG
- IgA
- IgE

Final Phases of B cell Differentiation are Mediated by Contact T cell signals (CD40L/CD40) and Lymphokines
The Hyper IgM Syndrome (HIM)

The Hyper IgM Syndrome (HIM) is an X chromosome-linked Ig deficiency characterized by low serum levels of IgG, IgA and IgE with normal numbers of circulating IgM expressing mature B cells. Germinal centers and splenic follicles due not develop.

Affected patients (usually males) are susceptible to pyogenic infections, autoimmune disease and lymphoproliferative disease. In addition, patients are also susceptible to Pneumocystis carinii infections.

The genetic defect in the majority of HIM patients is associated with mutations in the gene encoding CD40L and can be corrected functionally by soluble CD40 ligand, *in vitro*. A few HIM patients have normal CD40L but defects in CD40 signaling.

Major Functions of T Lymphocytes

(1) Induction and Activation of B cells (Help)- required for most antibody responses

(2) Delayed Type Hypersensitivity (DTH) - important in elimination of intracellular pathogens (virus, fungi and mycobacteria)

(3) Cell mediated Cytotoxicity (Killer function)- important in the immune response to virus infected cells and cancer cells

(4) Suppressor Cell Function- regulates the cell mediated and antibody responses
Delayed Type Hypersensitivity (DTH)

a. DTH is initiated principally by CD4+ Th1 cells and is the primary defense mechanism against intracellular parasites including the mycobacteria (TB), fungi and intracellular bacteria (Listeria monocytogenes).

b. The cognitive phase of DTH involves CD4+ T cell - macrophage/dendritic cell (MHC class II/peptide) interaction resulting in the local secretion of lymphokines.

c. The effector phase of DTH is effected by lymphokines which activate macrophages to secrete lysozyme, TNF, IL-1 and IL-12 as well as chemotactic and migration inhibitory factors restricting granulocytes, macrophages and eosinophils to the site of inflammation.
Physiology of the DTH Response

Infestation with Mycobacterium leprae can result in different clinical forms of leprosy. There are two polar forms: tuberculoid and lepromatous leprosy, but several intermediate forms also exist.

<table>
<thead>
<tr>
<th>Tuberculoid Leprosy</th>
<th>Lepromatous Leprosy</th>
</tr>
</thead>
</table>

Cytokine patterns in leprosy lesions:

\[
\begin{array}{c|c|c|c|c}
 & \text{T}_{1} \text{ cytokines} & & \text{T}_{2} \text{ cytokines} & \\
\hline
\text{Tuberculoid} & \text{Lepromatous} & \text{Tuberculoid} & \text{Lepromatous} \\
\text{IL-2} & & \text{IL-4} & \\
\text{IFN-}\gamma & & \text{IL-5} & \\
\text{TNF}\beta & & \text{IL-10} & \\
\end{array}
\]
Functions of Th subsets

**Th1 Cells**
- IL-2
- IFN-γ
- TNF

**Functions of Th1 subsets**
- Activate macrophages/dendritic cells
- Induce delayed type hypersensitivity (DTH) responses important in eradicating intracellular pathogens (TB, leprosy, listeria)
- Mediate Th1 diseases (e.g., rheumatoid arthritis, multiple sclerosis and type I diabetes)

**Th2 Cells**
- IL-4
- IL-10

**Functions of Th2 subsets**
- Help B cells and induce humoral immunity
- Mediate allergic and immediate hypersensitivity responses
- Involved in antibody mediated immune diseases like SLE and ITP

Summary

1. T cells are activated by APCs; MHC Class I activates CD8+ T cells and MHC Class II activates CD4+ T cells. Among the functions of these cells are helping B cells (Th cells), secreting cytokines (CD4+ and CD8+ T cells), and mediating cytotoxicity (CD8+ T cells, only).

2. The molecular basis of T cell help to B cells is CD40 on the B cells interacting with CD40 L on the T cells, and the secretion of cytokines (e.g., IL-4) from the T cells. This occurs in secondary lymphoid organs.

3. The signal transduction of T cells is complex, but involves early signals (protein tyrosine kinases, Ras-activated MAP kinases, and PLC. PLC is required for the production of IP₃, which triggers Ca²⁺-dependent activation of calcineurin and NF-AT, and DAG, which activates PKC and, ultimately, NF-κB.

4. Th cells can be polarized into Th1 or Th2 subtypes, defined by the cytokines they secrete. Learn these cytokines.

4. Delayed type hypersensitivity (DTH) is mediated by activated macrophages, and results in the secretion of Th1 cytokines (e.g., IFN-γ and IL-2). It is involved in many disease states, such as tuberculosis and tuberculoid leprosy.