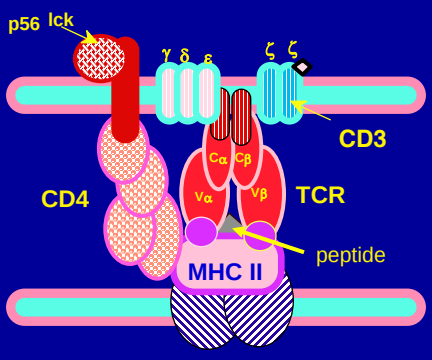
T Cell Effector Mechanisms I: B cell Help & DTH

Ned Braunstein, MD

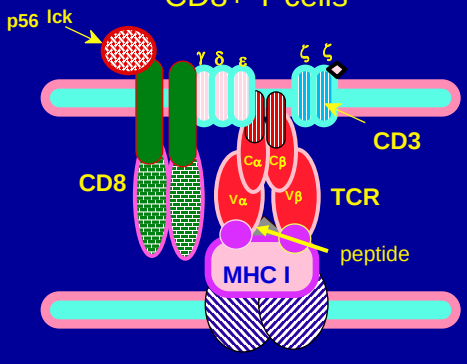
The Major T Cell Subsets

CD4+ T cells



(1) Interacts with MHC class II expressing cells (B cells, macrophages)
(2) Induce(help) B cells to synthesize antibody
(3) Induce and activate macrophages
(4) Secretes lymphokines

CD8+ T cells



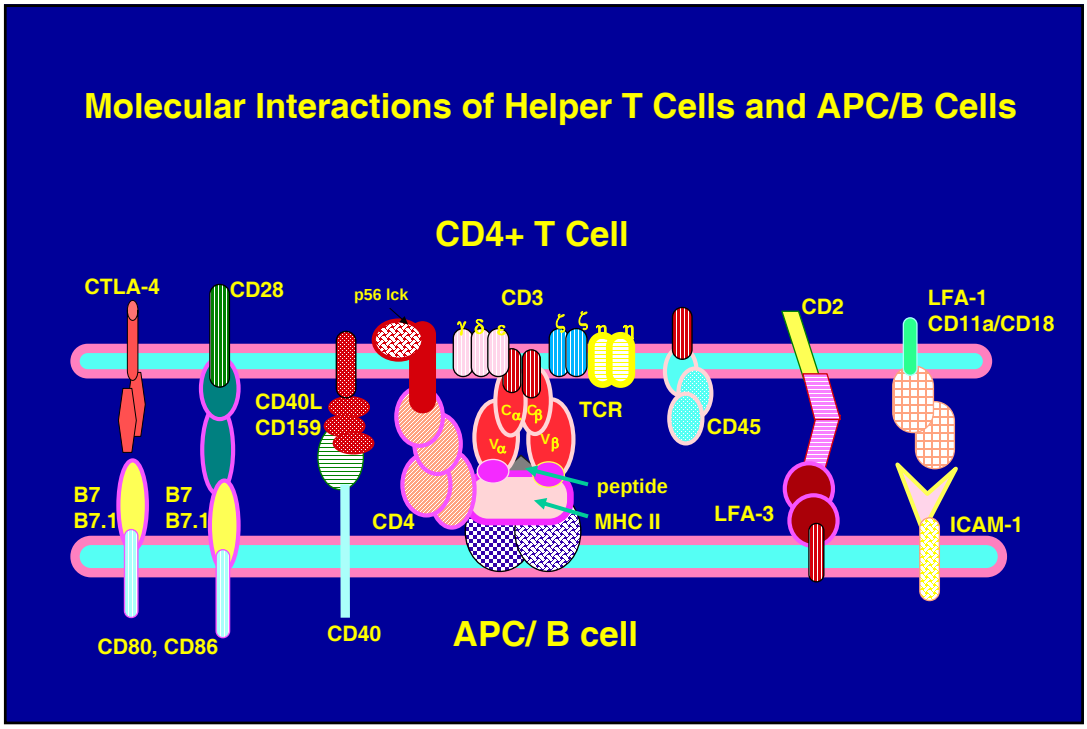
(1) Interacts with MHC class I expressing cells (all nucleated cells)
(2) Kill MHC class I expressing target cells
(3) Suppress immune responses
(4) Secretes lymphokines

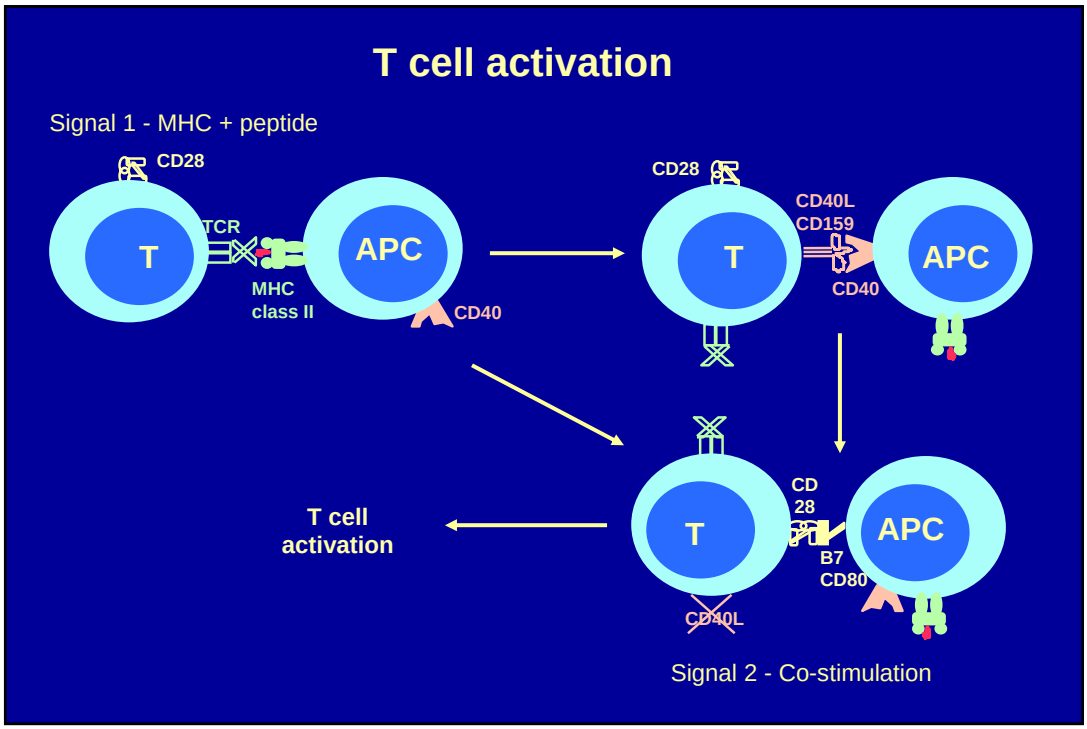
Observations

- 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

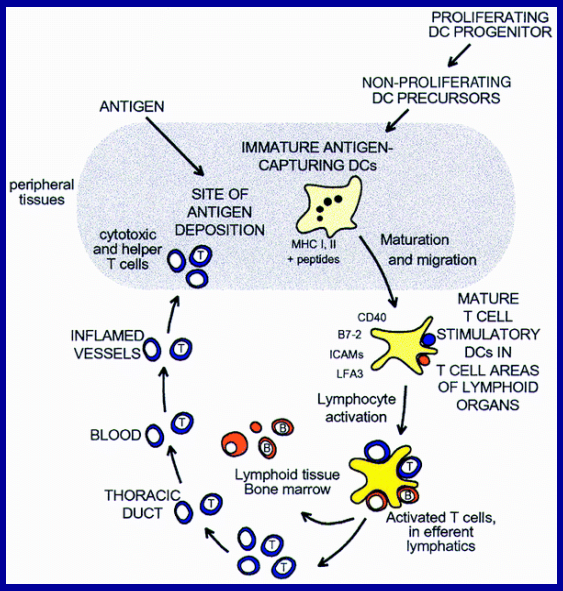
- T cell activation is highly regulated and involves both antigen plus context
  - APC
    - MHC molecule
      - antigen processing & presentation
    - Other cell surface molecules
      - accessory molecules and co-stimulators
  - Cytokines (and chemokines)


Molecular Interactions of Helper T Cells and APC/B Cells
CD4+ T Cell
CTLA-4
CD28
p56 lck
CD3
CD2
LFA-1
CD11a/CD18
CD40L
CD159
TCR
CD45
B7
B7.1
B7
B7.1
peptide
MHC II
CD4
LFA-3
ICAM-1
CD80, CD86
CD40
APC/ B cell


T cell activation
Signal 1 - MHC + peptide
CD28
TCR
T
APC
MHC
class II
CD40
CD28
CD40L
CD159
T
APC
CD40
T cell
activation
T
CD
28
APC
B7
CD80
CD40L
Signal 2 - Co-stimulation

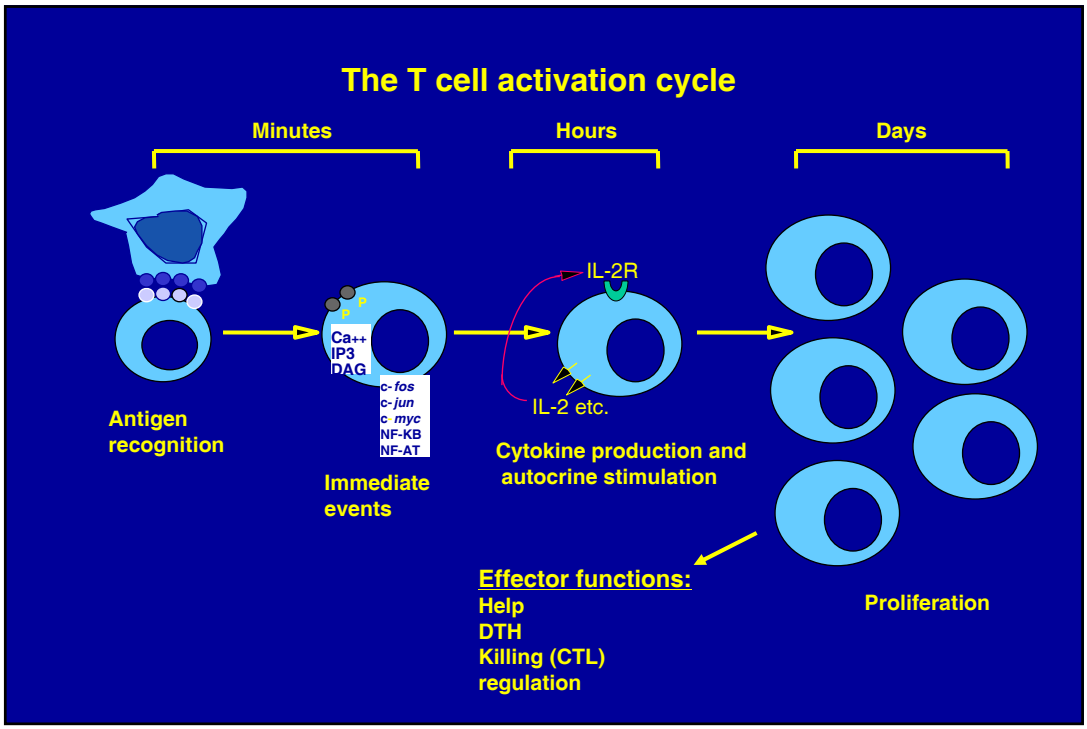
Naïve T cells are activated by DCs presenting antigen in LNs where they mature into effector cells

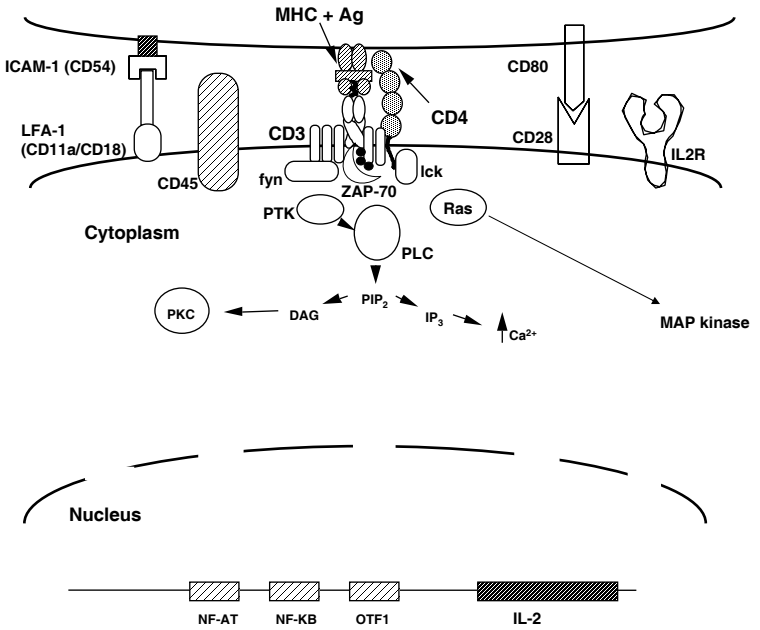
The Biology of Dendritic Cells: Antigen capture and presentation to T cells



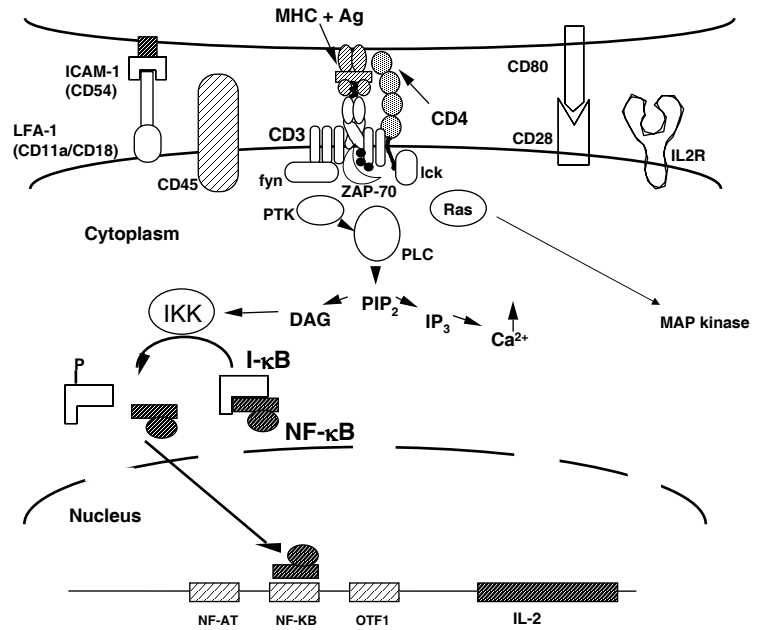
Antigens are captured by DCs in peripheral tissues and processed to form MHC-peptide complexes. As a consequence of antigen deposition and inflammation, DCs begin to mature, expressing molecules that will lead to binding and stimulation of T cells in the T-cell areas of lymphoid tissues. If the antigen 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
PLC: Phospholipase C-γ
Lck, fyn, ZAP-70: Protein tyrosine kinases
Ras: Low MW GTPase
CD45: A tyrosine phosphatase



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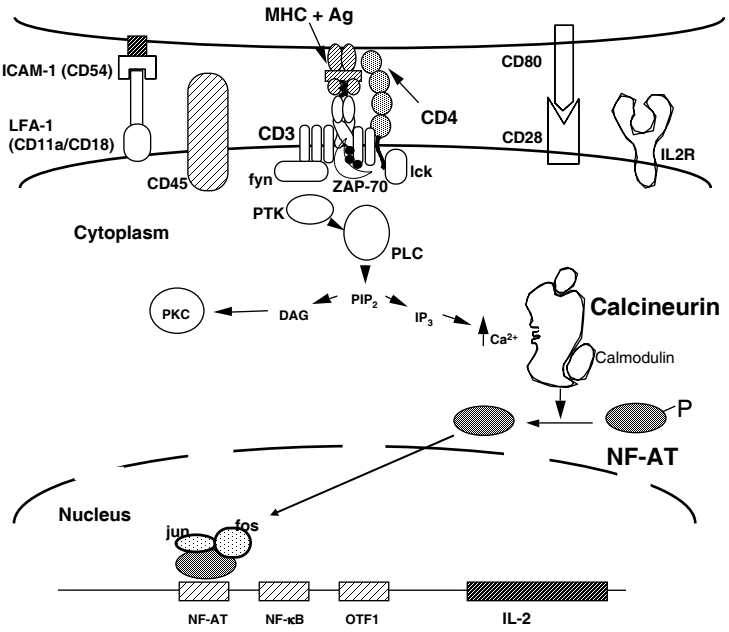
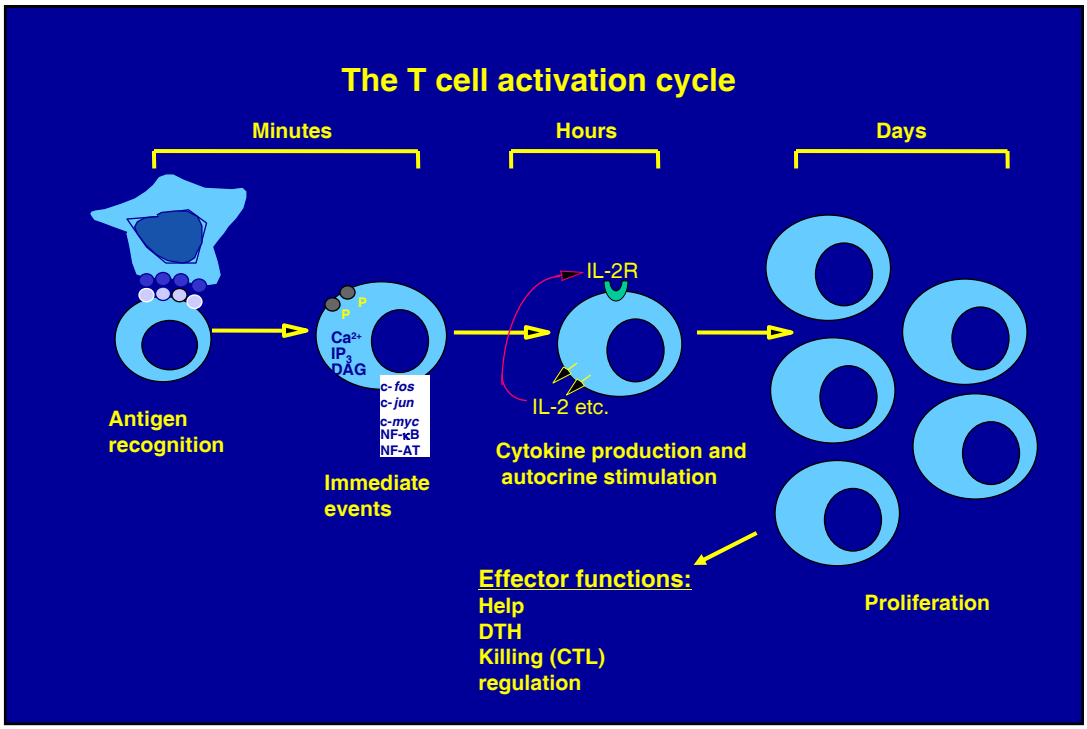
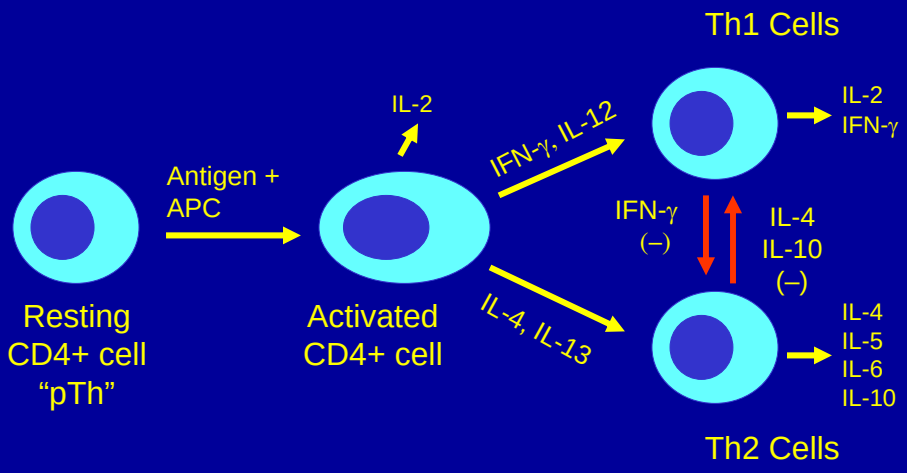


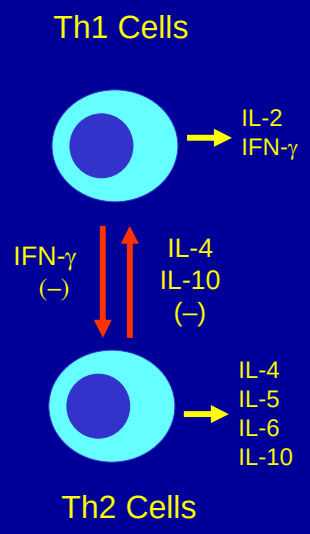
Calcineurin: A Ca^{2+}/calmodulin-activated protein phosphatase that dephosphorylates the transcription factor NF-AT, triggering its nuclear translocation, where it cooperates with other transcription factors (e.g., fos/jun) to trigger transcription (e.g., of IL-2 and its receptor)



Naïve CD4+ T cells differentiate into Th1 and Th2 subsets



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

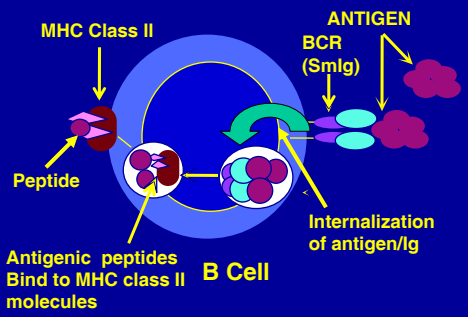
(1) Induction and Activation of B cells (Help)- required for most antibody responses

(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

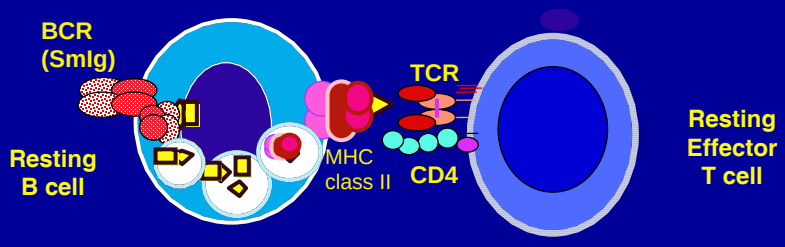
(4) Suppressor Cell Function- regulates the cell mediated and antibody responses

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

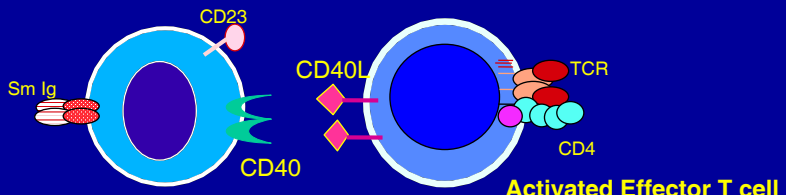


Antigen binds specifically to SmIg, is internalized into vesicles and cleaved into peptides which displace and bind to MHC class II molecules. The peptide/MHC complex is then transported to the surface membrane.

B Cell Help- Part II
Antigen Presentation and Initial Activation of CD4 T cell

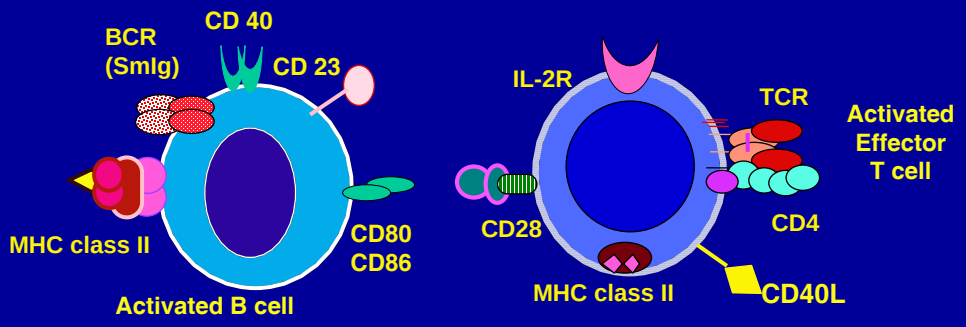


B Cell Help -Part III
B Cells Receive Signal 2 From T Cells via CD40

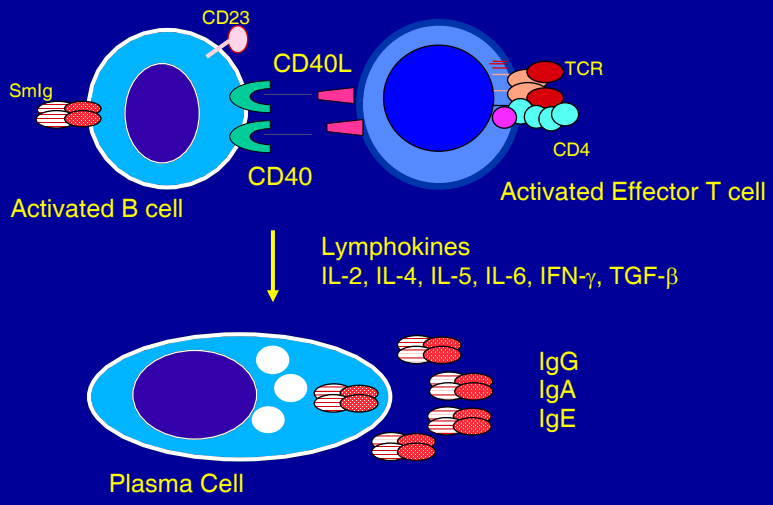


Triggering of B cell proliferation
Rescue from apoptosis
Induction of Ig isotype class switching
Up-regulation of CD80 and CD86
Germinal center formation
Up-regulation of CD23
Downregulation of CD40L expression

B Cell Help -Part IV
Activated B cells Express CD80 and Deliver Signal 2 to T cell



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 carini 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.

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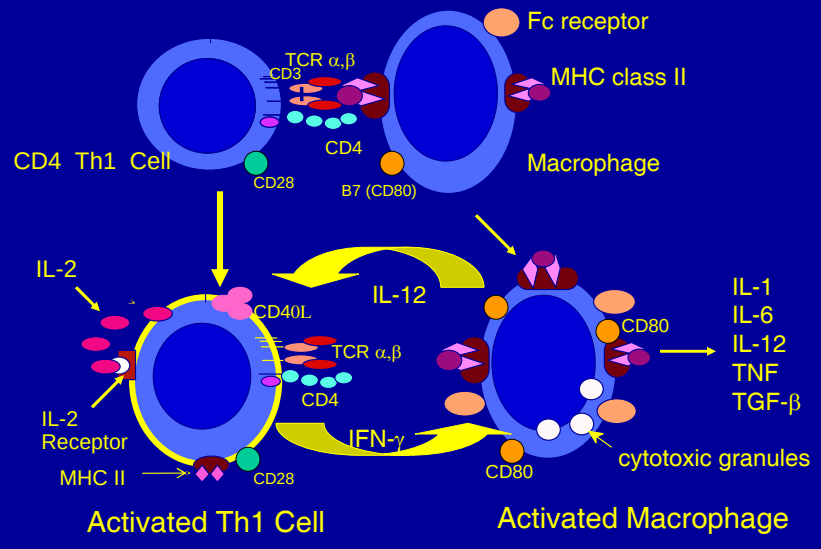
Delayed Type Hypersensitivity (DTH)

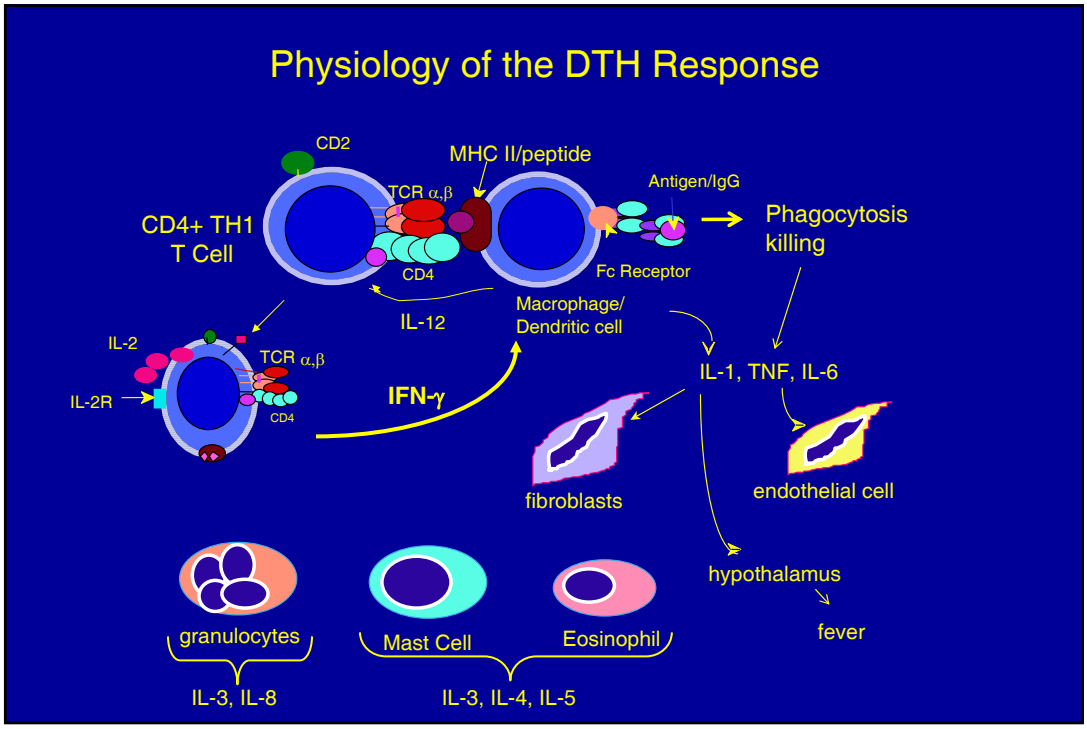
a. DTH is initiated principally by CD4+ Th1 cells and is the primary defense mechanism against intracellular parasites including the mycobacteria (TB), fungi and intracellular bacteria (listeriae monocytogenes).

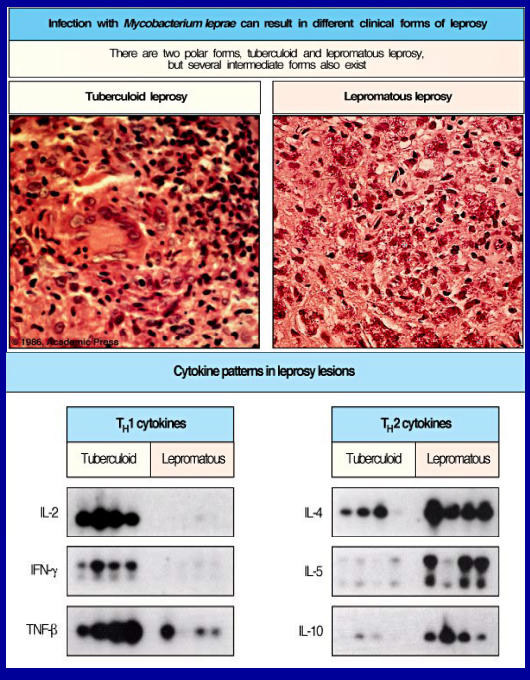
b. The cognitive phase of DTH involves CD4+ T cell - macrophage/dendritic cell (MHC class II/peptide) interaction resulting in the local secretion of lymphokines.

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.

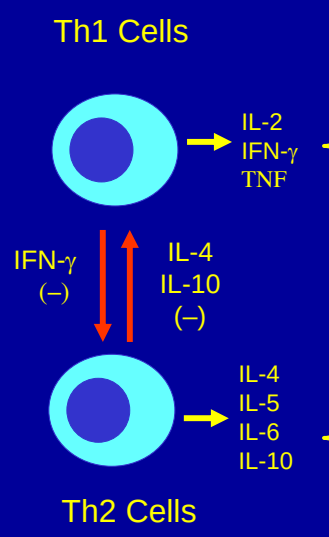
T Cell- Macrophage Interactions




Physiology of the DTH Response
CD2
MHC II/peptide
TCR α,β
Antigen/IgG
CD4+ TH1
T Cell
Phagocytosis
killing
CD4
Fc Receptor
IL-12
Macrophage/
Dendritic cell
IL-2
TCR α,β
IL-2R
CD4
IFN-γ
IL-1, TNF, IL-6
fibroblasts
endothelial cell
hypothalamus
fever
granulocytes
Mast Cell
Eosinophil
IL-3, IL-8
IL-3, IL-4, IL-5


Infection 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
Tuberculoid leprosy
Lepromatous leprosy
© 1986, Academic Press
Cytokine patterns in leprosy lesions
TH1 cytokines
TH2 cytokines
Tuberculoid
Lepromatous
Tuberculoid
Lepromatous
IL-2
IFN-γ
TNF-β
IL-4
IL-5
IL-10

Functions of Th subsets



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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 IP_3, which triggers Ca^{2+}-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.