

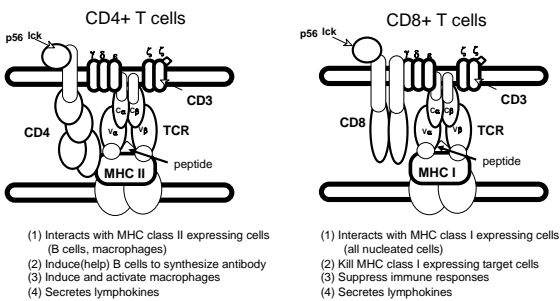
T Cell Effector Mechanisms I: B cell Help & DTH

Ned Braunstein, MD

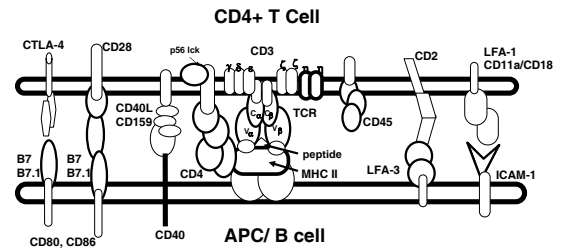
Implications/Overview

- 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)

The Major T Cell Subsets



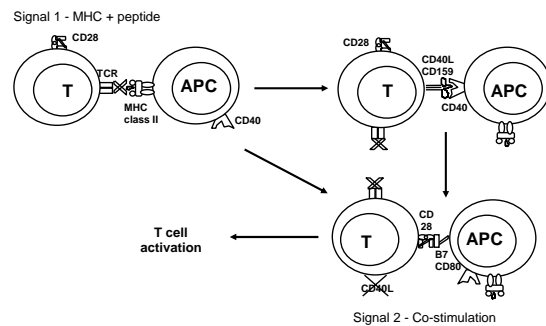
Molecular Interactions of Helper T Cells and APC/B Cells



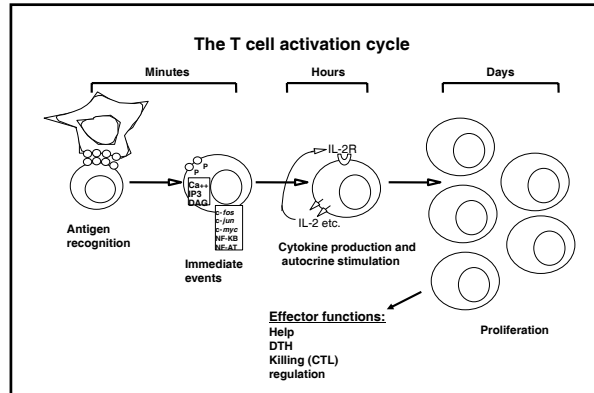
Observations

- 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

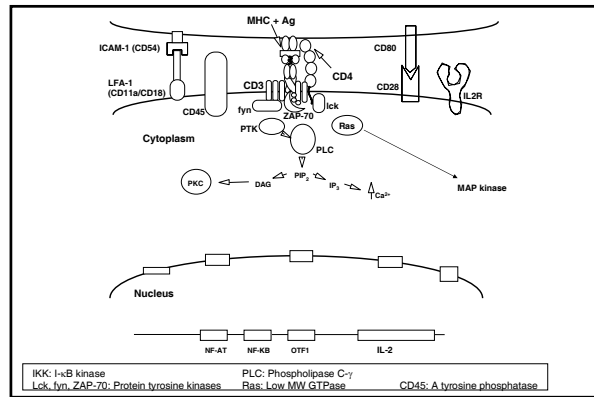
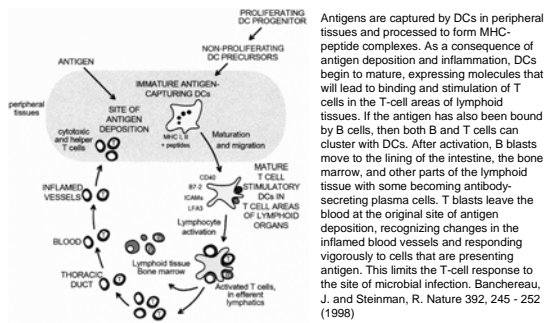
T cell activation



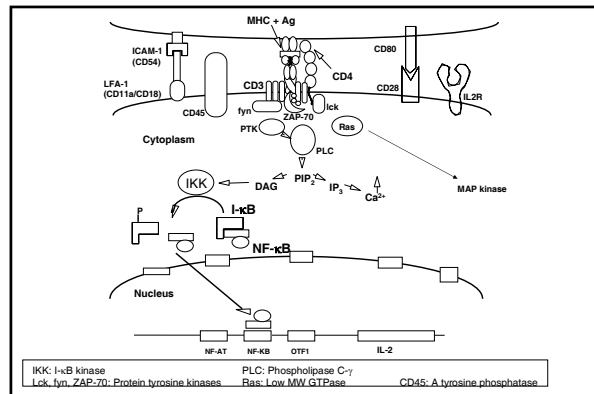
Naïve T cells are activated by DCs presenting antigen in LNs where they mature into effector cells

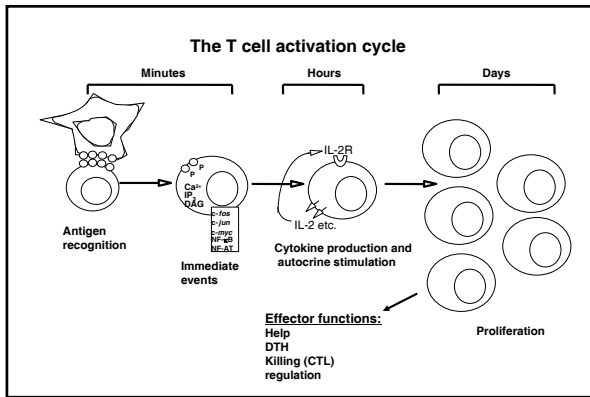
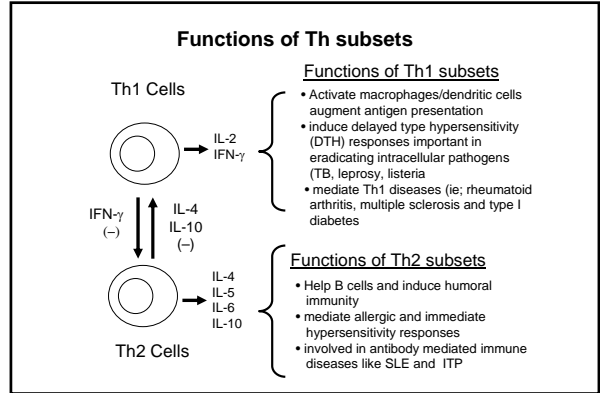
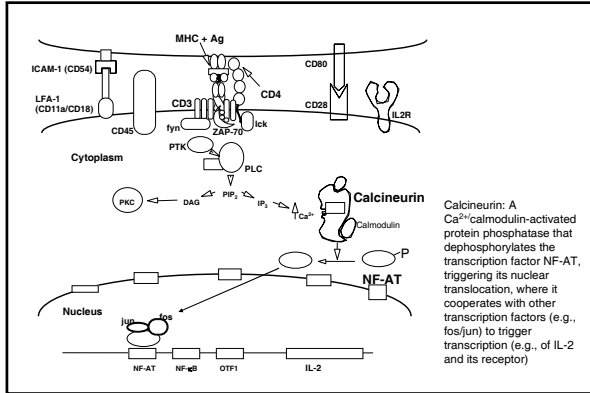


The Biology of Dendritic Cells: Antigen capture and presentation to T cells

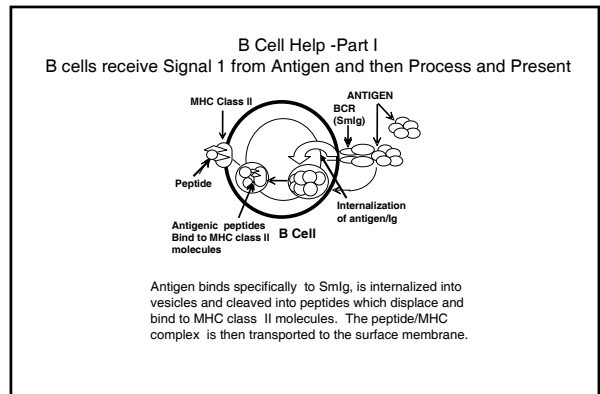
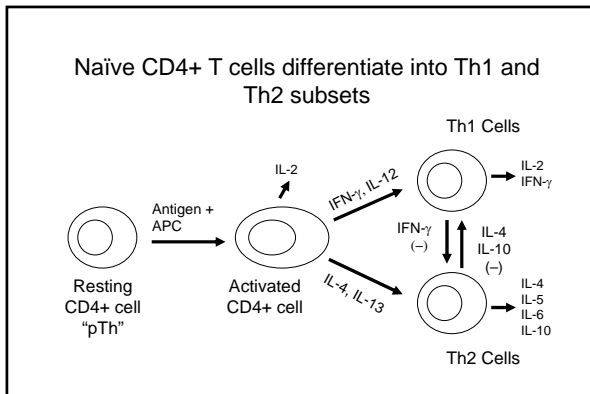


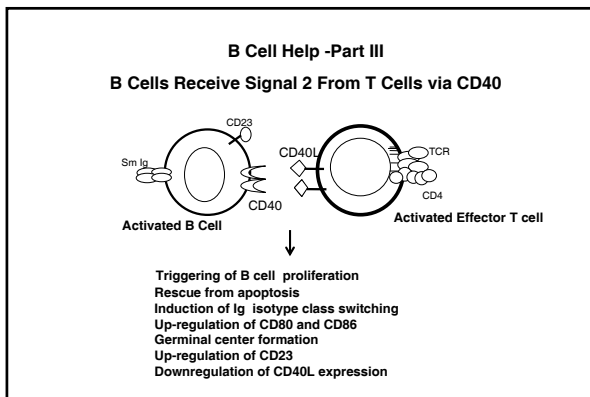
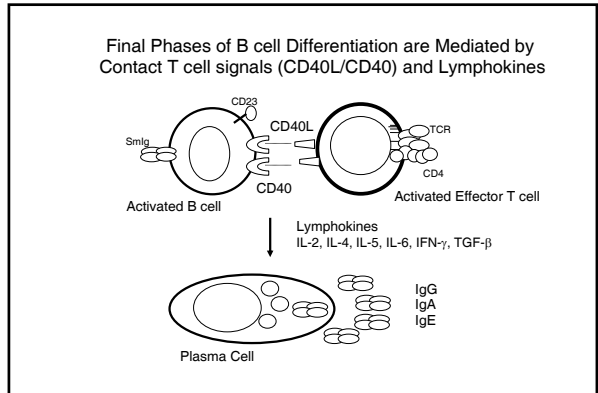
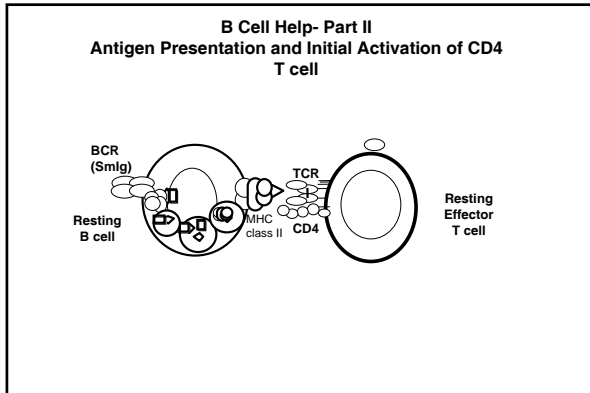
Primed effector T cells can be restimulated in tissue by antigen + MHC without requiring costimulation





- ### 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



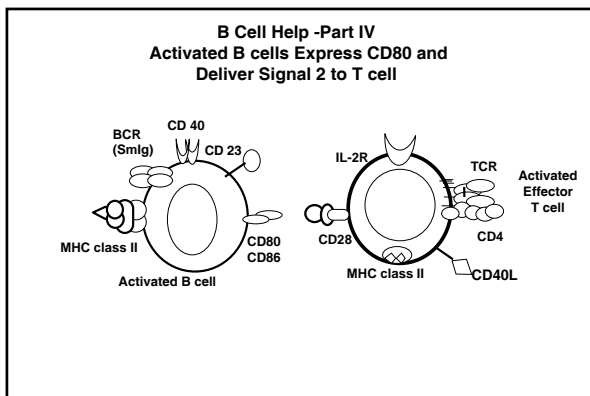


The Hyper IgM Syndrome (HIM)

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 do 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.



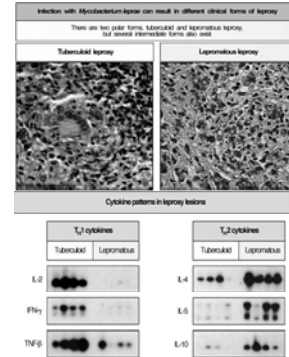
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Delayed Type Hypersensitivity (DTH)

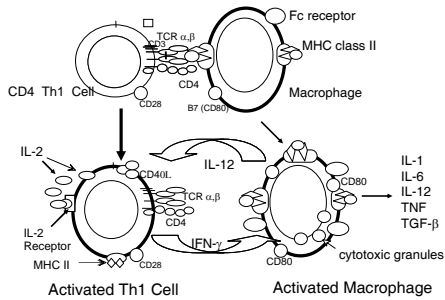
a. DTH is initiated principally by CD4+ Th1 cells and is the primary defense mechanism against intracellular parasites including the mycobacteria (TB), fungi and intracellular bacteria (listeria monocytogenes).

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.

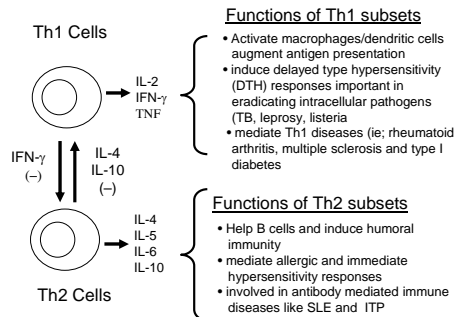
c. The effector phase of DTH is effected by lymphokines which activate macrophages to secrete lysozyme, TNF, IL-1 and IL-12 as well as chemotactic and migration inhibitory factors restricting granulocytes, macrophages and eosinophils to the site of inflammation.



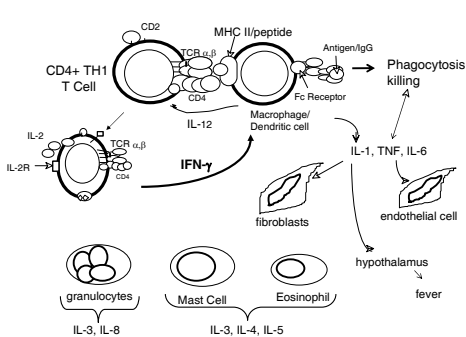
T Cell- Macrophage Interactions



Functions of Th subsets



Physiology of the DTH Response



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- κ B).
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.