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

1) Naïve T cells home continuously from the blood to lymph nodes and other secondary lymphoid tissues. Homing to lymph nodes occurs in high endothelial venules (HEV), which express molecules for the constitutive recruitment of lymphocytes.

2) Lymph fluid percolates through the lymph nodes; the fluid is channeled to them from peripheral tissues, where dendritic cells collect antigenic material. In inflamed tissues, dendritic cells are mobilized to carry antigens to lymph nodes, where they stimulate antigen-specific T cells. On stimulation, T cells proliferate by clonal expansion and differentiate into effector cells, which express receptors that enable them to migrate to sites of inflammation.

3) Although most effector cells are short-lived, a few antigen‐experienced cells survive for a long time. These memory cells are subdivided into two populations on the basis of their migratory ability: the effector memory cells migrate to peripheral tissues, whereas central memory cells express a repertoire of homing molecules similar to that of naïve T cells and migrate preferentially to lymphoid organs.
**The T cell activation cycle**

- **Minutes**
  - Antigen recognition
- **Immediate events** (immediate T cell responses)
  - Effector functions:
    - Help
    - DT
    - Killing (CTL) regulation
- **Hours**
  - Cytokine production and autocrine stimulation
- **Days**
  - Proliferation

**Key molecular interactions between T cells and APCs**

1. Induction of cytokines/chemokines (IL-8, IL-12, TNF-α, MIP-1α)
2. Stimulation of CD80 and CD86 expression and co-stimulatory function with activation of T cell growth
3. Augmentation of antigen-presenting function

**Naïve CD4+ T cells differentiate into Th1 and Th2 subsets**

- **Resting CD4+ cell 'pTh'**
- **Antigen + APC**
- **Activated CD4+ cell**
  - IL-2
- **Th1 Cells**
  - IL-2, IFN-γ, TNF
  - IL-12
  - IL-4, IL-10
- **Th2 Cells**
  - IL-4, IL-6, IL-10

**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, lyme)
- Mediate Th1 diseases (i.e., rheumatoid arthritis, multiple sclerosis, 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 (Helper)** - 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 Induction and Activation of B cells**

(Helper Function)

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

The CD4+ T cell α,β TCR/CD4 complex binds to the MHC class II/peptide complex on the surface of B cells. The CD4+ Th2 cells are triggered to secrete IL-2, IL-4, IL-5, IL-6 and IL-10 and begin to express CD40L. These lymphokine and contact dependent signals (CD40L) induce B cells to proliferate, class switch and differentiate into antibody (IgM, IgG, IgA and IgE) secreting B cells and plasma cells.

**Antigen Processing and Presentation by B cells**

Antigen binds specifically to BCR (surface membrane Ig), 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.

**Antigen Presentation by B cells**

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.

**Expression of Membrane Proteins Following Antigen Specific Activation of T and B Cells**

**CONSEQUENCES OF CD40L/CD40 INTERACTIONS DURING T-B CELL INTERACTIONS**

- Triggering of B cell proliferation
- Rescue from apoptosis
- Induction of Ig isotype class switching
- Germinal center formation
- Up-regulation of CD23
- Downregulation of CD40L expression
Lymphokines
IL-2, IL-4, IL-5, IL-6, IFN-γ, TGFβ

Plasma Cell

Final Phases of B cell Differentiation are Mediated by Contact T cell signals (CD40L/CD40) and Lymphokines

Activated B cell

Lymphokines
IL-2, IL-4, IL-5, IL-6, IFN-γ, TGFβ

Activated Effector T cell

IgG
IgA
IgE

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 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.

The Hyper IgM Syndrome (HIM) (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

Major Functions of T Lymphocytes

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 affected 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.

Th1 CD4+ T Cells Induce Inflammation and DTH

Th1 CD4+ T cells secrete lymphokines (IL-2, IFN-γ, IL-12, TNF-α) which activate macrophages and dendritic cells, leading to the release of proinflammatory cytokines and chemokines (IL-8, MCP-1). This results in the recruitment of inflammatory cells to the site of inflammation, contributing to the development of DTH.

DTH Pathway of Contact Hypersensitivity

Inflammation inducing CD40L/CD40 interactions

Proinflammatory molecules
Chemokines (IL-8, MCP-1)
Lymphokines (IL-1, GM-CSF, TNFα)
IFN-γ, IL-12, IL-6
NO, proteolytic enzymes, PGE2
T Cell- Macrophage Interactions

- CD4+ Th1 Cell
- Activated Th1 Cell
- Activated Macrophage
- CD28
- TCR α,β
- MHC class II
- CD80
- CD4
- IL-2
- IL-12
- IFN-γ
- TNF
- IL-6
- IL-12
- TGF-β
- IL-1
- IL-6
- IL-12
- TNF
- IL-10
- MHC II/peptide
- Fc Receptor
- Activated Macrophage
- Cytotoxic granules

Physiology of the DTH Response

- CD4+ Th1 T Cell
- IFN-γ
- Macrophage/Dendritic cell
- IFN-γ
- CD80
- CD4
- CD28
- TCRA,β
- IL-1, TNF, IL-6
- L-1, L-2, L-4, L-5
- Mast Cell
- Eosinophil
- IL-3, IL-4, IL-5
- Fibroblasts
- Endothelial cell
- Antigen/IgG
- Inflammatory cytokines
- Hypothalamus
- Fever
- Granulocytes
- IFN-γ
- TNF
- IL-2
- IL-10
- IL-4
- IL-10
- IFN-γ
- IL-2

Functions of Th subsets

**Th1 Cells**
- IFN-γ
- IL-2
- IL-12
- TNF

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- Activate macrophages/dendritic cells
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**Th2 Cells**
- IL-4
- IL-10

Functions of Th2 subsets
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