CELL MEDIATED IMMUNITY

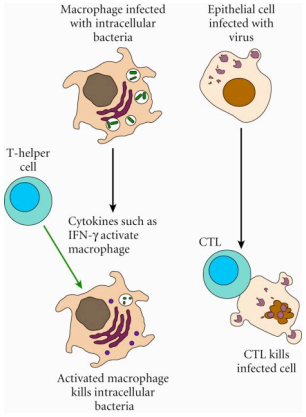
- Chapter 16

Cell Mediated Immunity

- Also known as Cellular Immunity or CMI
- The effector phase
  - T cells
    - Specificity for immune recognition reactions
    - TH provide cytokines
    - CTLs do the killing
  - Phagocytes
    - Kill or inactivate antigen

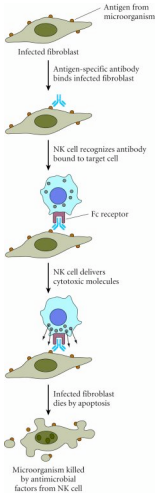
Basic Elements of Cell Mediated Immunity (CMI)

- TH cells can provide cytokines
  - to assist in the activation of macrophages
- CTLs can kill altered self cells
  - such as tumor cells
  - or virally infected cells



Antibody-dependent cell-mediated cytotoxicity (ADCC)

- Antigen specificity provided by antibody
- Antibody functions as a bridge between effector cell and and the target antigen
- Antibody Constant region Receptor (FcR) on NK cells recognizes Ab on "bad" cell
  - Release toxic chemicals to kill the cells
- Complement receptors (CR) on Neutrophils recognizes Ab on "bad" cell
  - Release toxic chemicals to kill the cells

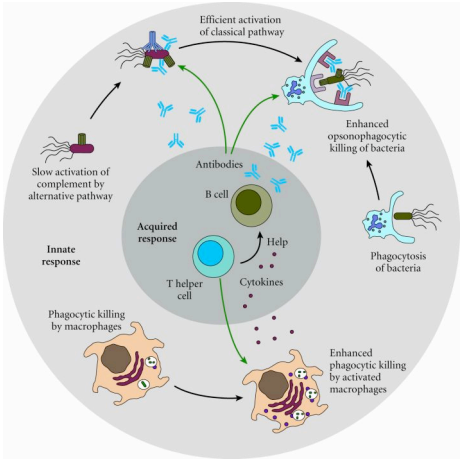


Antibody-dependent cell-mediated cytotoxicity (ADCC)

Specific Vs. Nonspecific Cell-Mediated Immunity

- Phagocytosis and complement activation are considered part of the innate or nonspecific immune response
- Products of the specific immune response can enhance the efficiency of these innate immune mechanisms
- Antibodies produced by B cells can mediate classical pathway complement activation and opsonize targets for enhanced phagocytosis
- T cells (TH1) enhance phagocytic killing by Mϕ by cytokines like IFN−γ

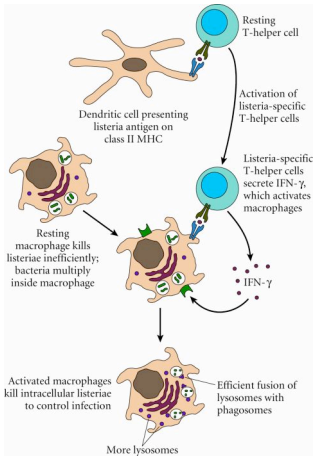
Specific Vs. Nonspecific Cell-Mediated Immunity



Mϕ Activation

- Enhances killing of newly phagocytized bacteria
- Enhances killing of intracellular pathogens like certain bacteria (Listeria) or intracellular parasites that would otherwise multiply unharmed
- Activation causes fusing of the lysosomes with the bacteria-laden vesicles and kills the bugs

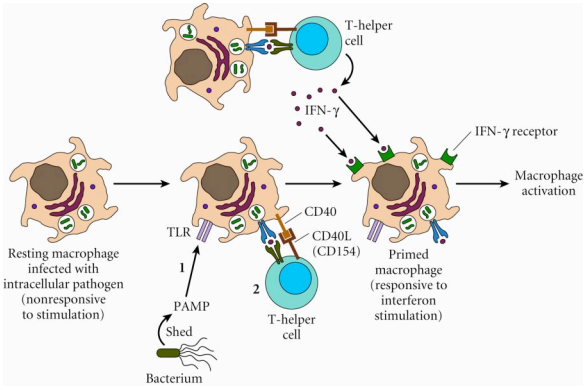
Mϕ Activation



Mϕ Activation

- By TH1 cell involves
  - Initial priming step and subsequent cytokine mediated step
- Priming is essential for making the macrophage responsive to the cytokine INF-γ
- Can occur by
  - Binding of Pathogen-associated molecular pattern (PAMP)
  - or by engagement of Mϕ CD40 protein by CD40L on TH cells

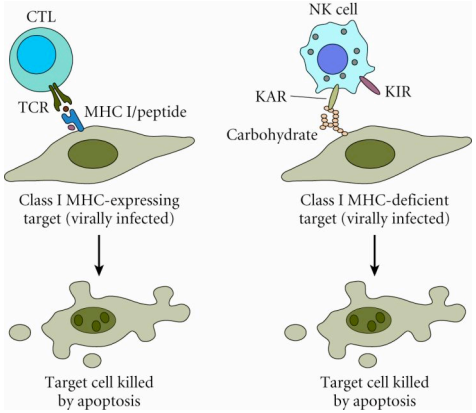
Mϕ Activation



CTLs and NK cells do cell-mediated Cytotoxicity

- CTLs do it with antigen specificity of T cell receptor (TCR)
- NK cells do it without antigen specificity
  - General mechanism of target cell recognition
  - Usually engage by killer activational receptor (KAR)
  - Binds to carbohydrates on target cell surface
- Killing can be stopped if
  - Killer inhibitory receptor (KIR) binds to MHC class I on target cell
  - Only kills cells with abnormal MHC class I on surface

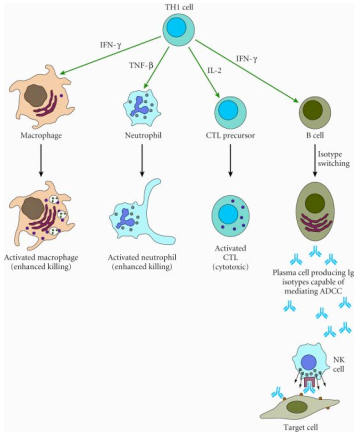
CTLs and NK cells do cell-mediated Cytotoxicity



TH1 cells orchestrate CMI

- Through the secretion of cytokines such as
  - IFN-γ, TNF-β/LT, and IL-2
- Enhances the activity of Mϕ, neutrophils, and CTLs
- Also by causing B cells to produce antibody isotypes capable of mediating ADCC

TH1 cells orchestrate CMI



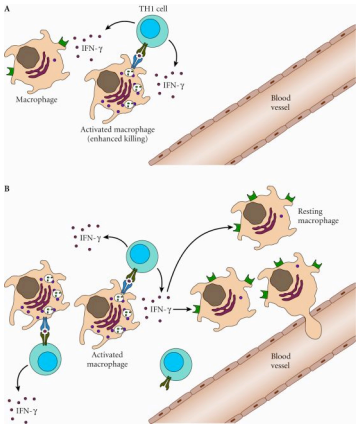
Delayed Type Hypersensitivity Reactions (DTH)

- DTH by definition:
- Immune reactions that show peak responses at 24-72 hours after antigen administration
- Are specific T cell responses to antigen
  - E.g. TB tests
- Immediate hypersensitivity reactions by definition:
- Immune reactions that that show within minutes of antigen administration
- Are antibody responses to antigen
  - E.g. allergies

Delayed Type Hypersensitivity Reactions (DTH)

- Sequential but overlapping phases of DTH
- 1 induction phase
  - Memory T cells recognize their MHC plus peptide complex presented by APC and are activated
- 2 inflammatory phase
  - Leukocytes extravasate and accumulate in the affected tissue
- 3 effector phase
  - Activated Mϕ kill the intracellular microbe
- 4 chronic DTH reaction
  - To certain persistent sources of antigen (mycobacteria) which are classically characterized by granuloma formation
- Granuloma
  - Walled off portions of tissue within which microbes are trapped causing tissue damage

Delayed Type Hypersensitivity Reactions (DTH)



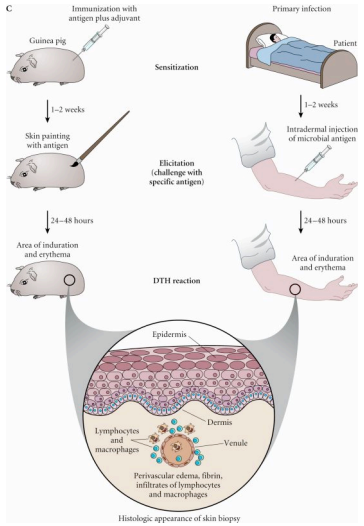
Mϕ phagocytize antigen and present it to TH1 cells

A) TH1 cells secrete cytokines that activate local mf and recruit more Mϕ and TH1 cells to area

B) If chronic antigen is present, a large mass of activated Mϕ and TH1 cells may form a granuloma

Delayed Type Hypersensitivity Reactions (DTH)

- DTH is only observed after induction of a T memory response by prior exposure (sensitization) to antigen
- In the lab this can occur by injection of antigen in to an animal
- In people this usually occurs by infection with a microorganism like TB.
- The secondary exposure to TB antigen to the skin on the TB test results in red and inflamed spot where antigen was administered

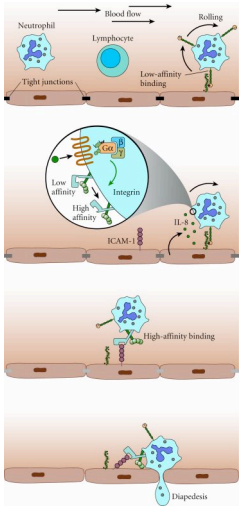


Delayed Type Hypersensitivity Reactions (DTH)

TB test

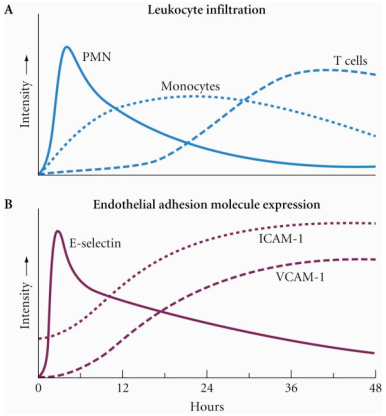
Extravasation of Leukocytes

- Leukocytes move from within the bloodstream to within the tissues
  - Through the blood vessel walls during inflammatory reactions
- Rolling adhesion by selectin-carbohydrate interactions
- Tight junctions dissociate
- Adhesion molecule expression increased
- Diapedesis occurs
  - Squeezing of of leukocyte between endothelial cells of blood vessel wall



Extravasation of Leukocytes

Extravasation of Leukocytes



Neutrophils (PMNs) are first to go through

Correlates with expression of E-selectin that binds to surface of PMNs

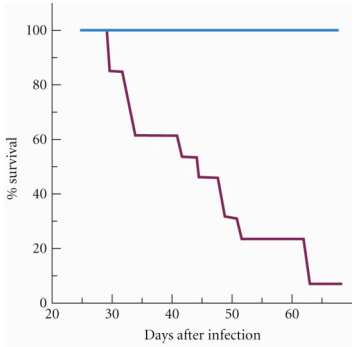
Delayed Type Hypersensitivity Reactions (DTH)

- CMI mediated through DTH is crucial for resistance to a variety of pathogenic microbes:
- Facultative intracellular bacteria
  - L. monocytogenes
  - M. tuberculosis
- Fungi
  - Candida species
  - Histoplasma capsulatum
    - Cryptococcus neoformans
- Protozoan parasites
  - Leishmania major
  - Toxoplasma gondii
- Helminthic pararsites
  - Schistosoma mansoni
- Recovery from viral infections….

CMI mediated through DTH is crucial for resistance to intracellular pathogens

- Infect mice with Mycobacterium bovis
- Normal mice kill the bacteria due to an effective TH1-mediated DTH response (Blue line)
- IFN-γ deficient mice that cannot mount a TH1-mediated DTH response die of overwhelming infection within weeks (Red line)

CMI mediated through DTH is crucial for resistance to intracellular pathogens



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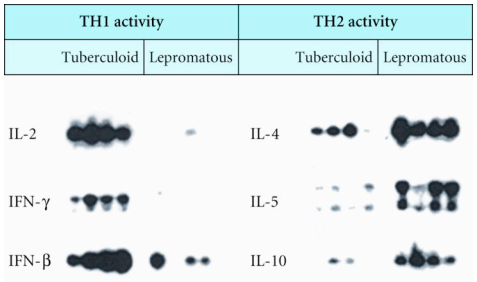
The 2 different forms of leprosy correlate with the TH cell polarity of the immune response

- TH1 and TH2 cell immune responses
- TH1
  - Properly contained or tuberculoid infection
- TH2
  - Ineffective immune response and widely disseminated or lepromatous infection

The 2 different forms of leprosy correlate with the TH cell polarity of the immune response



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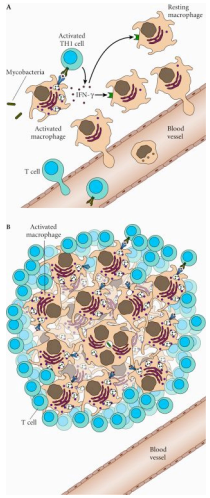
TH1 = Properly contained or tuberculoid infection

- The TH1 phenotype correlate with the less severe form of leprosy because
- TH1 cytokines recruit and activate macrophages
  - Chemotactic cytokines recruit
  - IFN-γ activates
- Results in the formation of a granuloma
  - contains the infection.

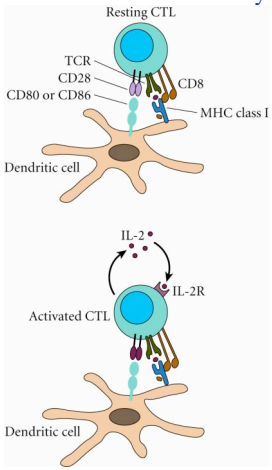


TH1 =
Properly contained
tuberculoid infection

Cytotoxic T Lymphocytes (CTLs)

- CD8+ T cells
- MHC class I restricted
- T cell mediated cytolysis of target cells but not nearby normal cells
  - Virus infected cells
  - Tumor cells
  - Intracellular bacteria
  - Intracellular parasites

Direct Activation of a naïve CD8+ CTL precursor
by a virus-infected DC



- Signal 1 from TCR-MHC w/viral peptide)
- Signal 2 from CD28-CD80/86 on DC
- CTL then produces both IL-2 and IL-2R
- Autocrine Stimulated CTL activation

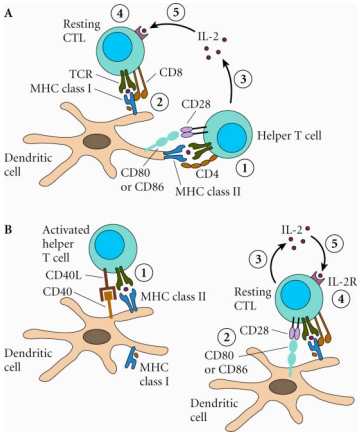
Indirect Activation of a naïve CD8+ CTL precursor by T helper (TH) cells

- CTL and TH cells are activated by a DC
- TH cell provides additional IL-2 for the IL-2R on the CTL for paracrine stimulated CTL activation

OR

- TH cell activates the DC so that when a CTL interacts, it receives both signal 1 and signal 2 necessary for activation

Indirect Activation of a naïve CD8+ CTL precursor by T helper (TH) cells



Paracrine activation

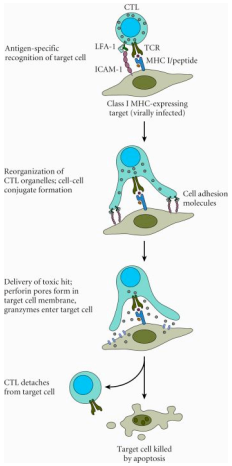
DC activation by TH

CTL Effector Phase: Lytic Mechanisms

- CTL-mediated cytolysis
- 5 stages in the CTL lytic cycle

1. Initial CTL binding to the target cell
   - MHC class I for CD8+ T cell lysis
   - MHC class II for CD4+ T cell lysis
2. Multiple TCR-MHC interactions and CTL activation
3. CTL introduction of the "lethal hit" via activation of the target cell's apoptosis or through a "toxic hit"of chemicals
4. Recycling of CTLS for additional attacks
5. Target-cell death once the CTL has detached

Stages of CTL-mediated cytolysis

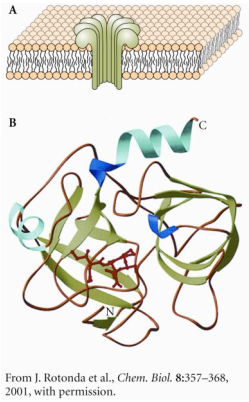


1. Intitial binding
2. Strengthening
3. Toxic hit
4. Detach and recycle
5. Target cell death

Toxic Hit: Perforin and Granzymes

- Perforin
  - Released from cytoplasmic granules of CTL
  - Forms pores in the target cell membrane
  - Allows granzymes to enter target cell
  - May cause osmotic lysis as well
- Granzymes
  - Protein molecules that activate key mediators of apoptosis
  - Some are also toxic to the actual intracellular microbe as well
    - granulysin
- Primarily used for lysis of intracellular microbe infected target cells

Toxic Hit: Perforin and Granzymes



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Hypothesized perforin pore

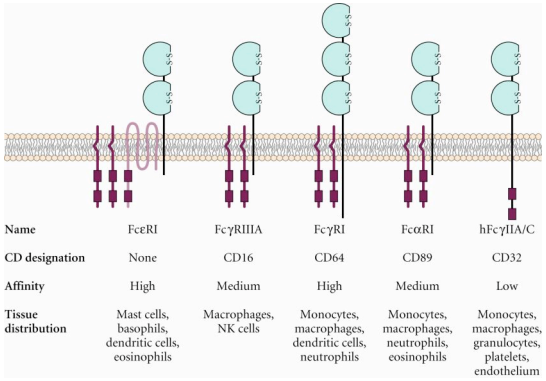
Structure of Granzyme B

Fc Receptors

- Fc Receptors bind to Immunoglobulin
- (Antibody molecules)

FcRs function for the phagocytosis of Ab coated particles by macrophages and killing of Ab coated particles by NK cells.

Fc Receptors



Name	FcεRI	FcγRIIIA	FcγRI	FcαRI	hFcγIIA/C
CD designation	None	CD16	CD64	CD89	CD32
Affinity	High	Medium	High	Medium	Low
Tissue distribution	Mast cells, basophils, dendritic cells, eosinophils	Macrophages, NK cells	Monocytes, macrophages, dendritic cells, neutrophils	Monocytes, macrophages, neutrophils, eosinophils	Monocytes, macrophages, granulocytes, platelets, endothelium

Fc Receptors