Immunology

728-655

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This lecture is an immunology overview and will be used as a foundation for the immunology pharmacotherapy lectures and lab over the next few weeks. No specific drug therapy will be presented. However, understanding the terminology, physiology, and clinical labs will be critical for this section of the course.

Learning Objectives

- Understand the integration of the cellular and soluble components of the immune system
- Differentiate between innate and adaptive immune responses
- Discuss the role of human leukocyte antigen (HLA) in antigen presentation.
- Differentiate among the types of T cells—both cell markers and function
- Choose laboratory tests that will assist with evaluation of immune system function
- Design an ELISA to detect antigen-specific antibody

Reading Assignment

Watch this animated video on TLR and immune response. It has more details that you are required to know, but it shows animated interactions between pathogens and components of the immune system.
https://www.youtube.com/watch?v=iVMIZy-Y3f8

Perform the virtual ELISA test for SLE (autoimmune lecture).
http://www.hhmi.org/biointeractive/immunology-virtual-lab Click on Launch Interactive button just below the title.
A link for a worksheet appears on the right side of the page. Please use it if it helps you follow along.

Human leukocyte antigen (HLA) is the human version of the major histocompatibility complex (MHC). These glycoproteins are present on cell surfaces and are critical in antigen presentation and recognition of self versus non-self.
The majority of the self-assessment questions align with the content of the lecture.

Study questions:

1. What are the differences among a monocyte, dendritic cell, and macrophage?
2. What are differences in function of T cells and B cells?
3. Does a positive ELISA test for Lyme disease indicate infection?

Phylogeny of the Immune System

- Innate vs. adaptive
- Cellular vs. humoral
- Hallmarks of the immune system
    - Redundancy
    - Diversity
    - Self vs. non-self discrimination
    - Memory
    - Mobility
    - Replication
    - Specificity

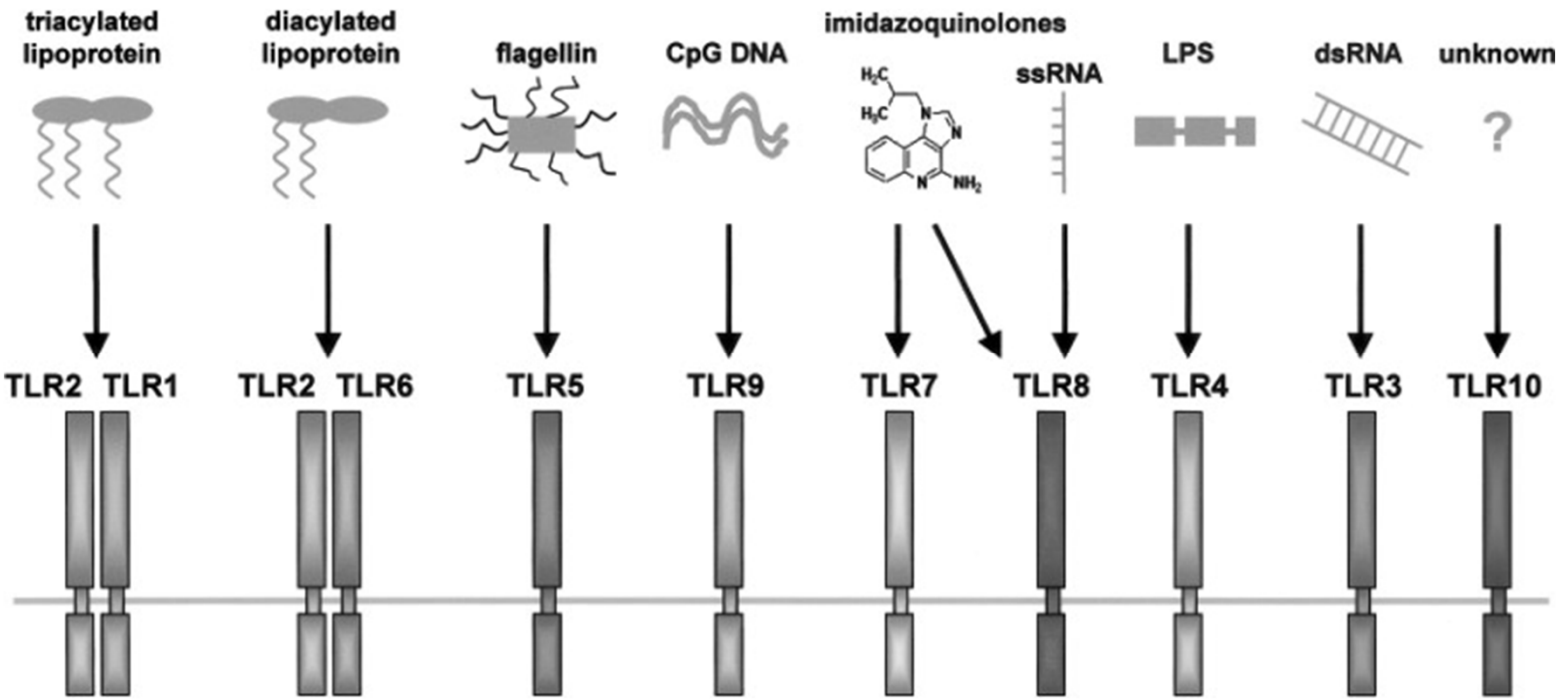
Innate Immunity

- Physical barriers
  - Skin
  - Cilia, mucous
  - Acidic pH of stomach
- Cells
  - Monocytes --Macrophages --Dendritic cells
  - Neutrophils --Eosinophils
  - Natural killer cells
- Complement

Pathogen Recognition

- Recognize PAMPS with PRR
  - Pathogen associated molecular patterns
    - Repetitive structures (bacterial flagella, DS RNA, nucleotide CpG, many more)
  - Pattern recognition receptors
- DAMPs: danger-associated molecular patterns
- Toll like receptors
  - Recognize patterns indicative of pathogen
  - Located on cell surface or in endosomes
  - Results in production of interleukin-1

TLRs

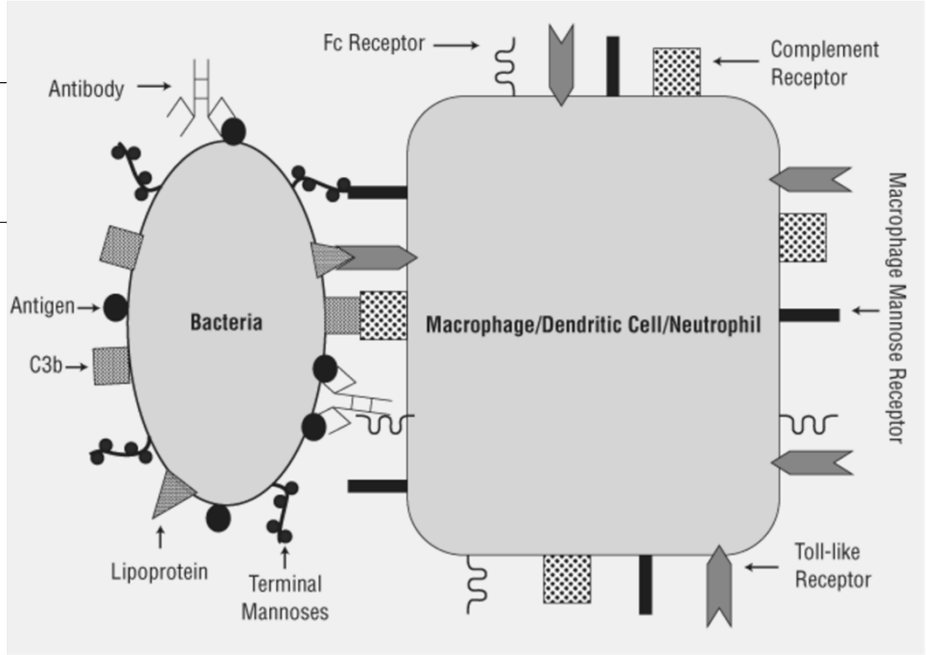


J Invest Dermatol 2005; 125(1): 1-8

Characteristics of Innate Immunity

- Rapid response, hours
- No memory
- No antigen specificity

From: eChapter 102. Function and Evaluation of the Immune System
Pharmacotherapy: A Pathophysiologic Approach, 11e, 2020



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:* www.accesspharmacy.com

Legend:

Phagocytosis of bacteria by macrophages, dendritic cells (DCs), and neutrophils. Macrophages, DCs, and neutrophils recognize bacteria opsonized (coated) with antibody or complement (C3b). On the surface of macrophages, DCs, and neutrophils reside receptors for antibody (Fc receptors) and complement (CR1, CR3, CR4). In addition, these cells may recognize the bacteria by pattern recognition receptors on the surface of macrophages, DCs, and neutrophils. Pattern recognition receptors include toll-like receptors, scavenger receptors, and mannose receptors.

Which of the following describes how Toll-like receptors recognize immunologic threats?

a) Microscopic identification
b) Through T cell receptors
c) Genetic polymorphisms
d) Pattern recognition

Complement Characteristics

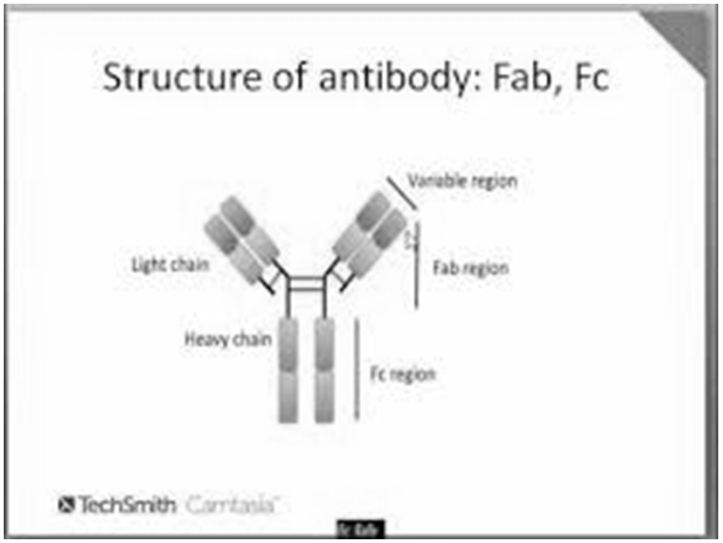
- Composed of at least 20 proteins that are always present in the blood
- No cells are in the system
- Part of both innate and adaptive immune system
- Threat activates complement on the surface of the pathogen

Complement Activation

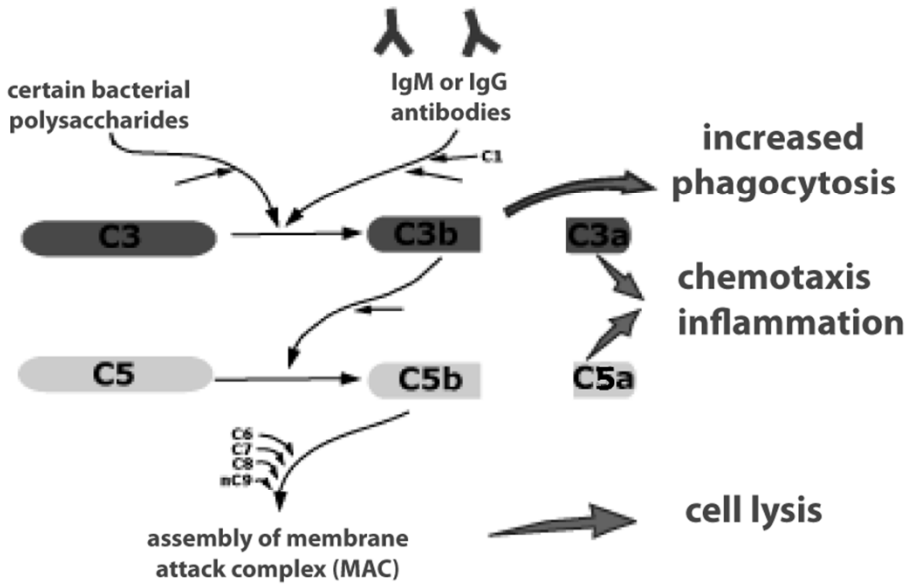
- Innate immune response
- Bacterial surface component (for example polysaccharide)

Complement Activation

- Adaptive immune response
- Antibody binds to antigen on cell surface
- Fc allows C1 to bind

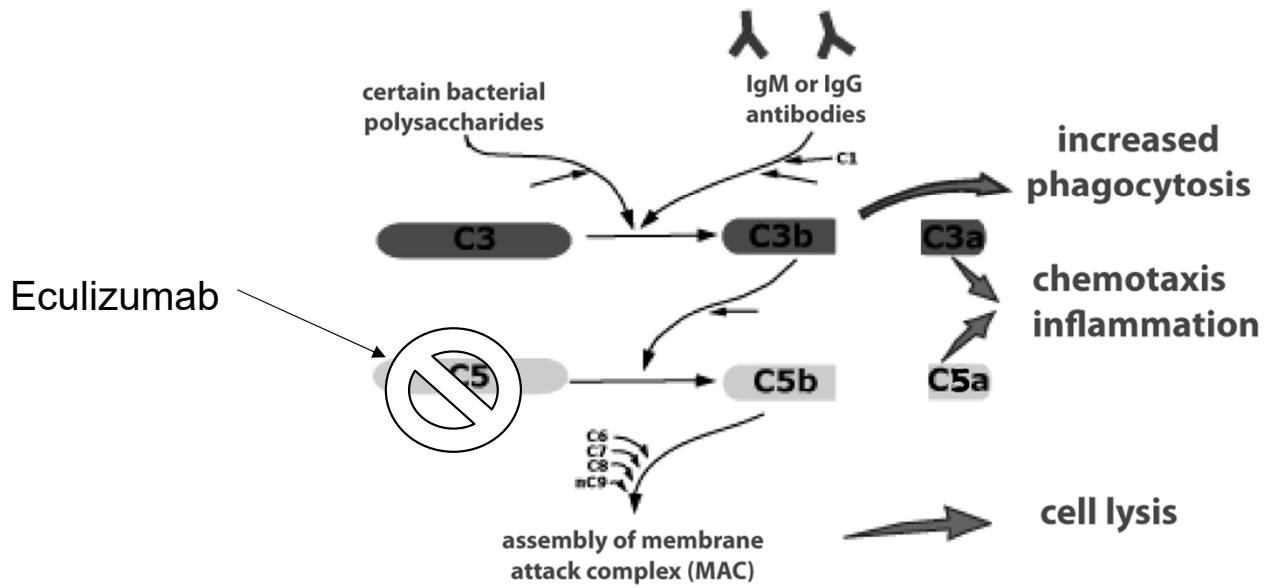


Complement System



https://courses.washington.edu/conj/inflammation/complement.htm

Complement System



https://courses.washington.edu/conj/inflammation/complement.htm

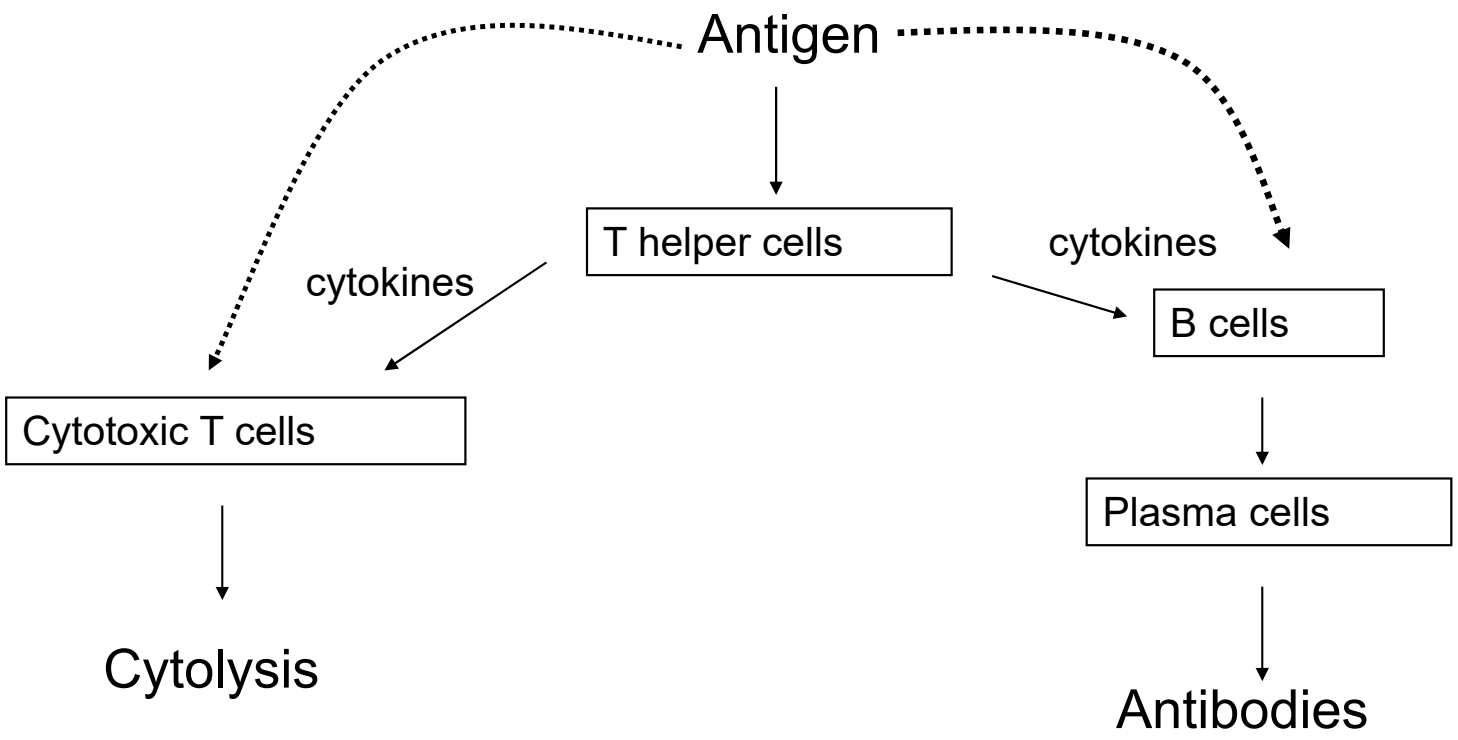
Janus Kinases (JAK)

- Tyrosine kinases that interact with cytokine receptors for intercellular signaling that results in regulation of gene expression

Adaptive Immunity

- B lymphocytes
  - antibodies
- T lymphocytes
  - Cytokines

Immune System



Characteristics of Adaptive Immunity

- Antigen specific
- Memory

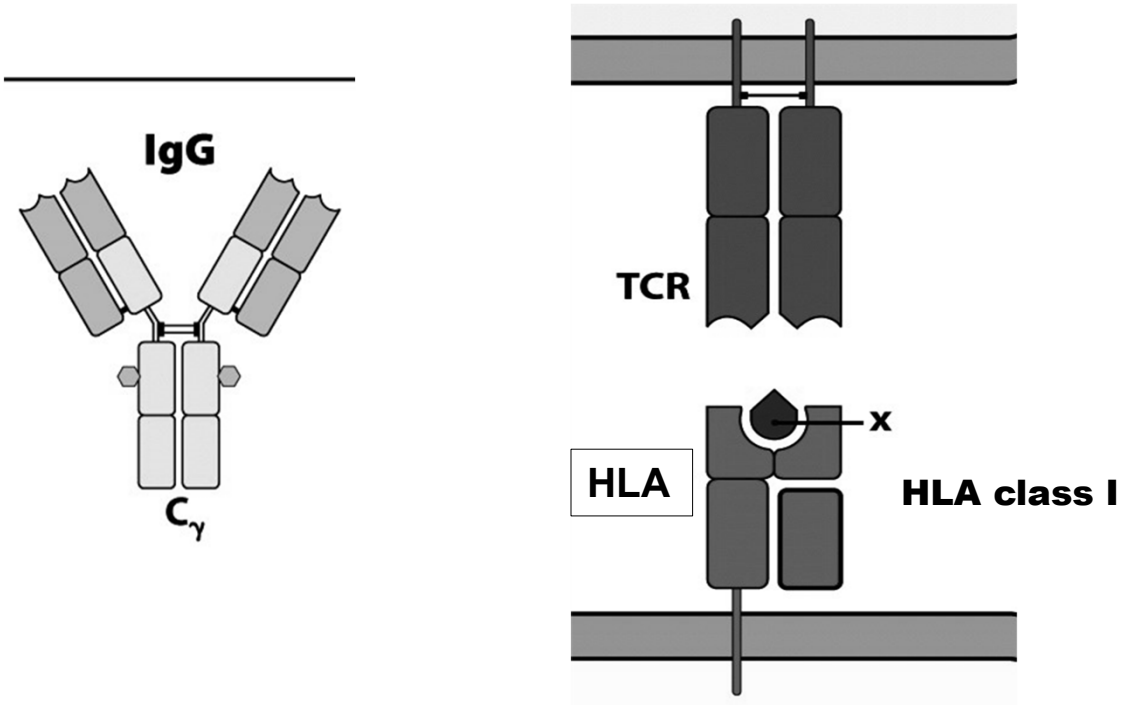
Adaptive Immunity Diversity

- Molecular mechanisms for gene rearrangements
- Many polymorphisms
    - Human leukocyte antigen (HLA)
    - Cytokines and receptors

Characteristics of Adaptive Immunity

- Response delayed (~7-10 days)
- Antigen specific
- Memory
- Structurally similar components
  - Human leukocyte antigens (HLA)
  - T cell receptors
  - Antibodies

Structurally Similar



B cells

- Act as antigen presenting cell
- Produce antibodies
    - Antigen recognition
    - T cell stimulation
- Activated B cells
    - Plasma cells
    - Memory B cells

T cells

- Cluster of differentiation: cell surface molecule used. Monoclonal antibodies can be used to identify CDs. Hundreds identified so far
- CD4+
    - T helper cells
- CD8+
    - T suppressor cells
    - Cytotoxic T cells
- CD3
    - All T cells

T cell Diversity

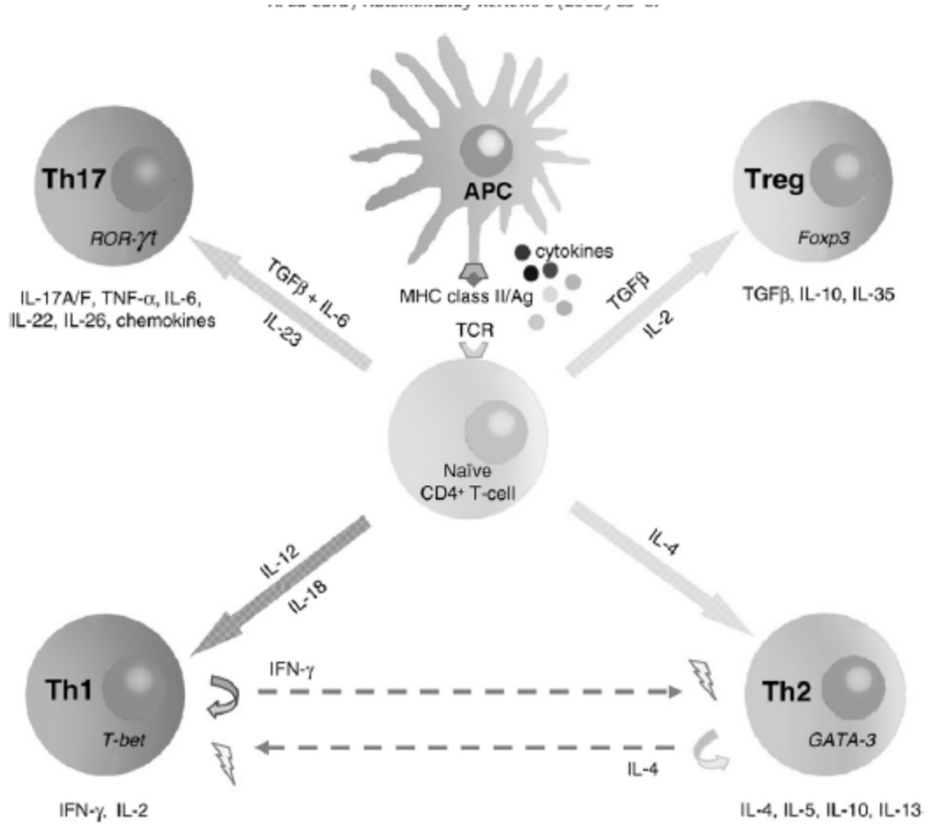
- Same principles as B cell diversity
  - Will cover in Immunoglobulins lecture
- Approximate number of combinations: 10^{18}

T Helper Cells

Several types

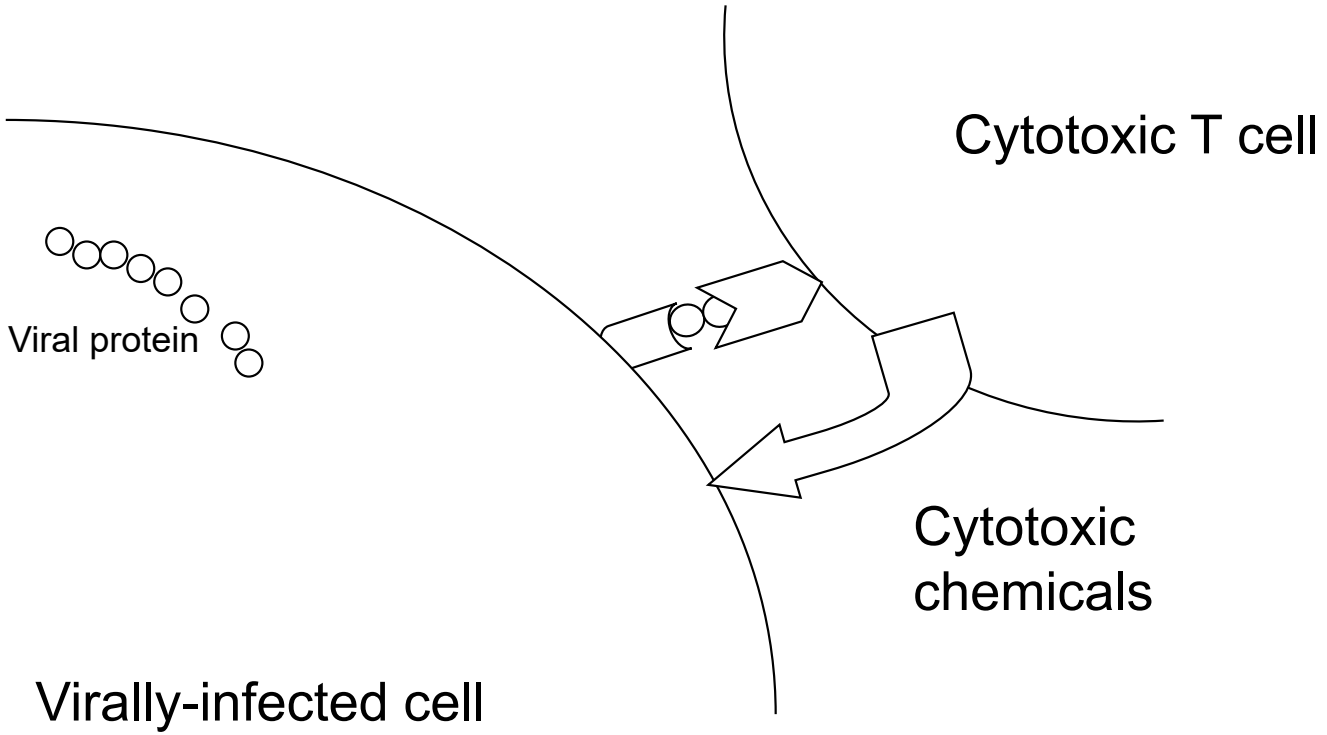
- Th1 cells: Produce interferon-γ and interleukin-2 and stimulate cytotoxic T cells
- Th2 cells: Produce interleukin-4,-5,-13 and stimulate B cells to produce antibodies
- Th17 cells: Produce interleukin-17 and act in host defense and autoimmunity
- Treg cells: Produce transforming growth factor β and moderate the effect of other immune cells

Th cells



La Cava A, 2008

Cytotoxic T Cell Response

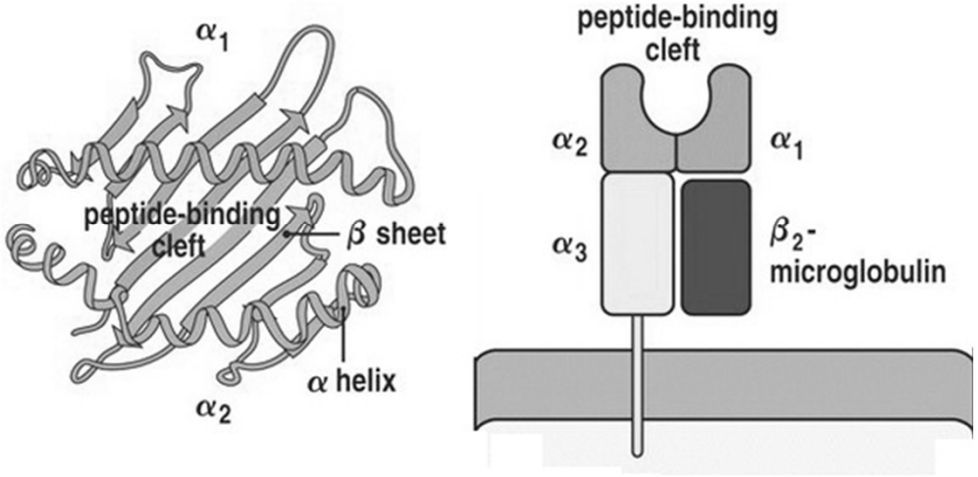


Which of the following cells is the prototype for response to a viral infection?

a) Th2
b) Cytotoxic T cell
c) PRR
d) B cell

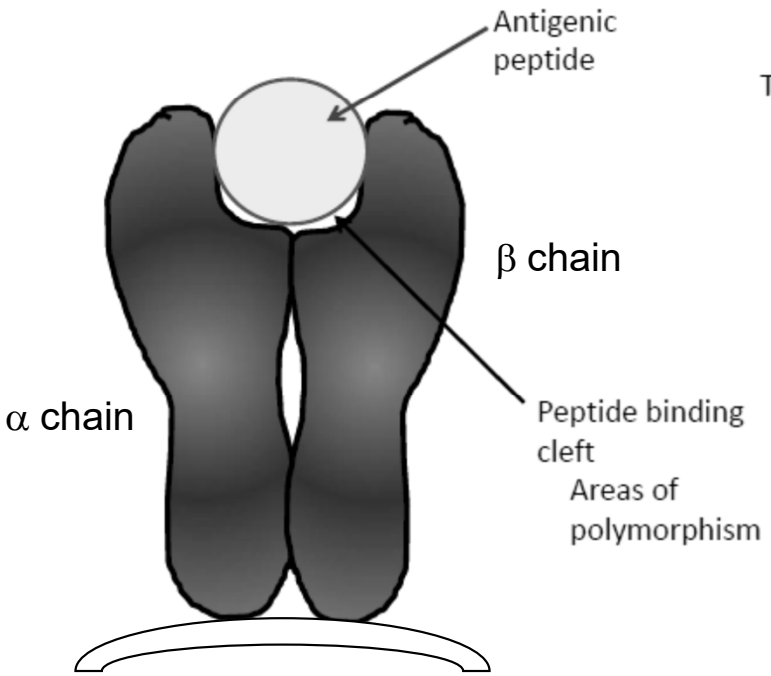
Human Leukocyte Antigen

- Human leukocyte antigen (HLA)
- Class I
    - On all nucleated cells
    - Associated with β2 microglobulin
    - Polymorphic
    - HLA-A, HLA-B, HLA-C
    - Present endogenous peptides
    - Activate CD8+ cells

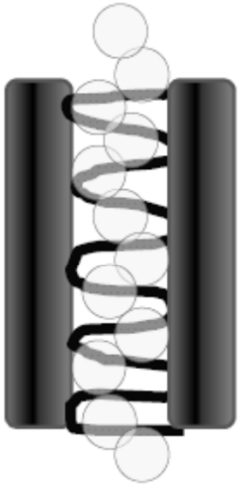

α1
peptide-binding cleft
β sheet
α helix
α2
peptide-binding cleft
α2
α1
α3
β2-microglobulin

Human Leukocyte Antigen

- Class II
  - On antigen presenting cells
    - B cell
    - Dendritic cell
    - Macrophage
  - α chain and β chain
  - Polymorphic
  - HLA-DR, HLA-DQ, HLA-DP
  - Present exogenous peptides
  - Activate CD4+ cells



Top view of the peptide binding cleft



Areas of polymorphism found within the peptide binding cleft of HLA

HLA Polymorphism

- Survival of the species
- Disease susceptibility
    - Infectious
    - Autoimmune
- Solid organ transplantation
- Bone marrow transplantation

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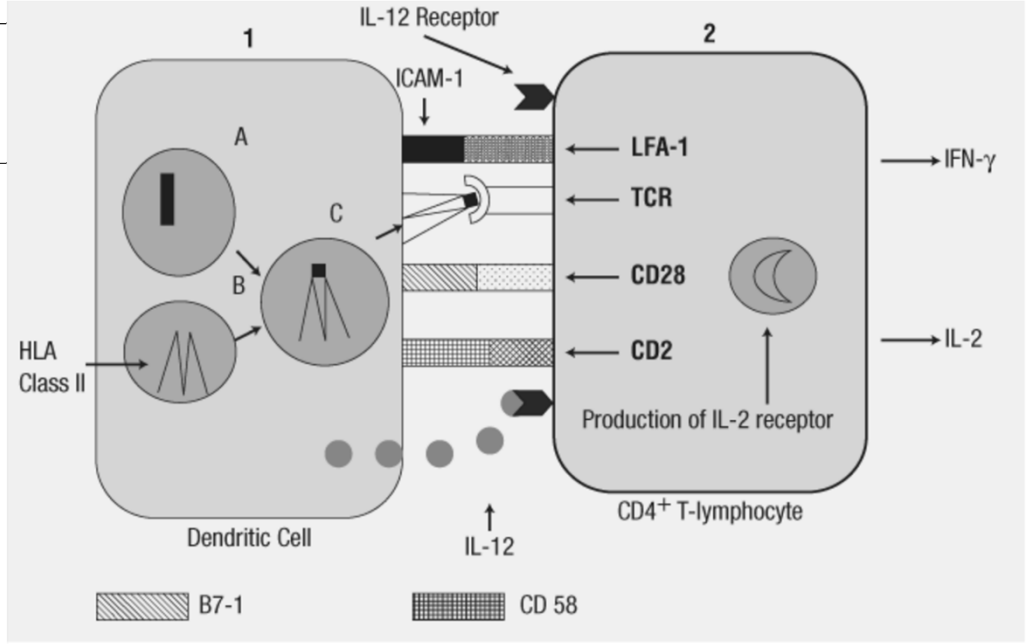


Legend:

Induction of T-helper type 1 (TH1) response. 1. The APC, in this case a DC, engulfs the pathogen by any of numerous cell surface receptors. After phagocytosis of the bacteria by the DC (A), the pathogen is digested into small peptides and become associated with major histocompatibility (MHC) class II within the endosome (B). Finally, the MHC class II plus peptide is expressed on the surface of the DC (C). The activated DC also secretes interleukin (IL)-12. 2. Naïve CD4+ T-lymphocyte activation requires the T-cell receptor (TCR) to recognize the antigenic peptide in association with MHC class II as well as the B7-1 (CD80) binding to CD28. The binding of CD2-CD58 and LFA-1 (CD11a/CD18) allows adherence between the T lymphocyte and DC. Upon activation, the TH1 CD4+ T lymphocyte secretes IL-2 and interferon (IFN)-γ and increases the production and expression of the IL-2 receptor. (ICAM, intercellular adhesion molecule).

What would be different if the naïve T cell matured into a Th2 cell?

Cytokines

- Mediators of communication within the immune system and for the immune system
- Paracrine and autocrine activities
- Overlapping functions
- Cytokine polymorphisms emerging are of research and clinical interest

Interleukin-1

- Production initiated by TLR
- Can breach blood brain barrier
- Fever

Interferon γ

- Activation of macrophages, natural killer cells
- Up regulation of HLA I, II expression

Interleukin-2

- Activation of lymphocytes, natural killer cells
- Autocrine activity; produced by activated T cells resulting in proliferation

Tumor Necrosis Factor α

- Mediator of inflammation
- Activates neutrophils, macrophages
- Prothrombotic activity
- Induces production of other cytokines
- Similar activities as IL-1

Interleukin-6

- Produced by B and T cells and macrophages
- Activated B cells
- Proinflammatory mediator
    - Simulates production of other cytokines
    - Stimulates production of CRP

Interleukin-12

- Inflammatory cytokine that regulates innate immunity
- Promotes production of IFNγ and Th1 type response
- Mediator of autoimmunity

Interleukin-23

- Inflammatory cytokine that regulates innate immunity
- Promotes Th17 response
- Enhances T cell memory and angiogenesis

Interleukin-17

- Produced by Th-17 cells
- Early in immune response to infection
    - Amplifies inflammatory response
- Role in autoimmunity

Which of the following matches the cytokine with its function?

a) IL-1—fever
b) IL-4—cytotoxicity
c) IL-6—hair growth
d) IFNγ—IgE production

White Blood Cell Count

- WBC
- Normal 5000-10,000 cells/mm^3
- Elevation nonspecific finding
    - Infection
    - Leukemia
    - Autoimmune disease
    - Drugs
- May not increase in very old and very young

Differential Blood Cell Count

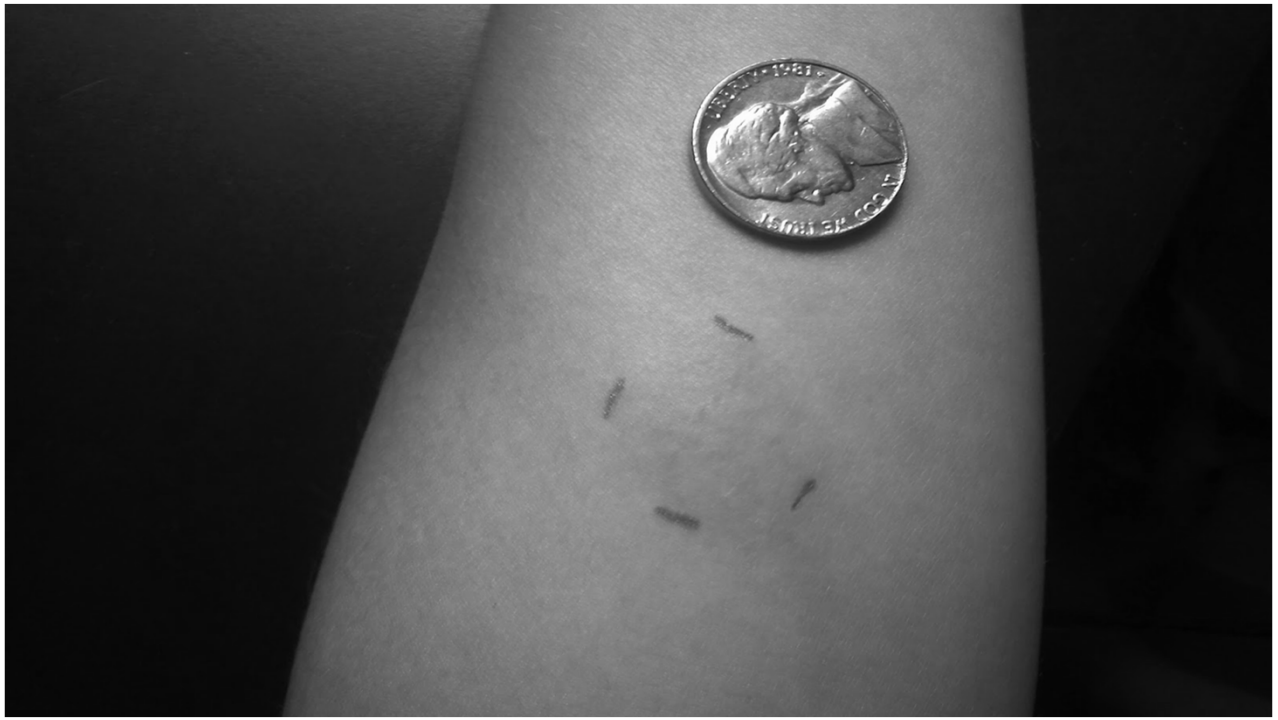
- Polymorphonuclear leukocytes 50-70%
- Immature neutrophils 3-5%
- Lymphocytes 20-40%
- Monocytes 0-7%
- Eosinophils 0-5%
- Basophils 0-1%

Left Shift

- Leukocytosis during acute infection
- More immature neutrophils (band > 10-20% of total WBC)
- Mature neutrophils=segs (segmented nucleus)

Lymphocytes

- Lymphocytosis
    - Frequently associated with viral infections
- Lymphopenia
    - HIV, particularly decreased CD4+ cells



Delayed Type Hypersensitivity

Test of competency of cell-mediated immunity

Common antigens used: PPD, tetanus toxoid, candida

Cluster of Differentiation

- CD
- Cell surface markers
- CD3 T lymphocytes
- CD4 T helper cells, monocytes, macrophages
- CD8 CTL, NK cells
- Cells labeled with monoclonal antibodies and counted using flow cytometry

Immune Globulin

- Total using serum protein electrophoresis
- Hypergammaglobulinemia
    - Chronic inflammatory conditions
    - Multiple myeloma
- Antigen specific
    - Often measured by ELISA
    - Examples: viral hepatitis, Lyme disease, measles

ELISA

Common technique. See web site on cover page for review of this procedure.