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Host Response to Infection: The Immune Response and Vaccination

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Section A

Introduction to Innate Immunity

The Immune System

- Central to survival after infection
- Central to public health
  - Immunity can be manipulated to protect both individuals and populations by vaccination
- Effective use of vaccination depends upon knowledge of immune system function
  - Nature of the vaccine (live, subunit, vectored)
  - Characteristics of the type of immunity induced
  - Target antigens

Innate Immunity

- Inborn
- Effective without prior exposure to an infectious agent
  - Nonspecific
- "First-line" defense

Continued

Innate Immunity

- Physical barriers
  - —Skin
  - —Cornea
  - —Mucus layers (with clearance)
  - —Outflow (urine, for example)
- Chemical barriers
  - —Stomach acid
  - —Fatty acids on skin
  - —Lysozyme in tears
- Active mechanisms
  - —Intracellular
    - Interferons
    - Apoptosis
  - —Organismal
    - Complement
    - Phagocytosis

Phagocytosis

- Active process that destroys invading pathogens
- Mediated by specialized cells (phagocytes)
  - Macrophages, neutrophils
- Phagocytes engulf potential pathogens
  - Efficient engulfment depends on receptors for common bacterial cell wall components
- Once engulfed, pathogens are killed and digested
- Some pathogens are resistant (TB)

Continued

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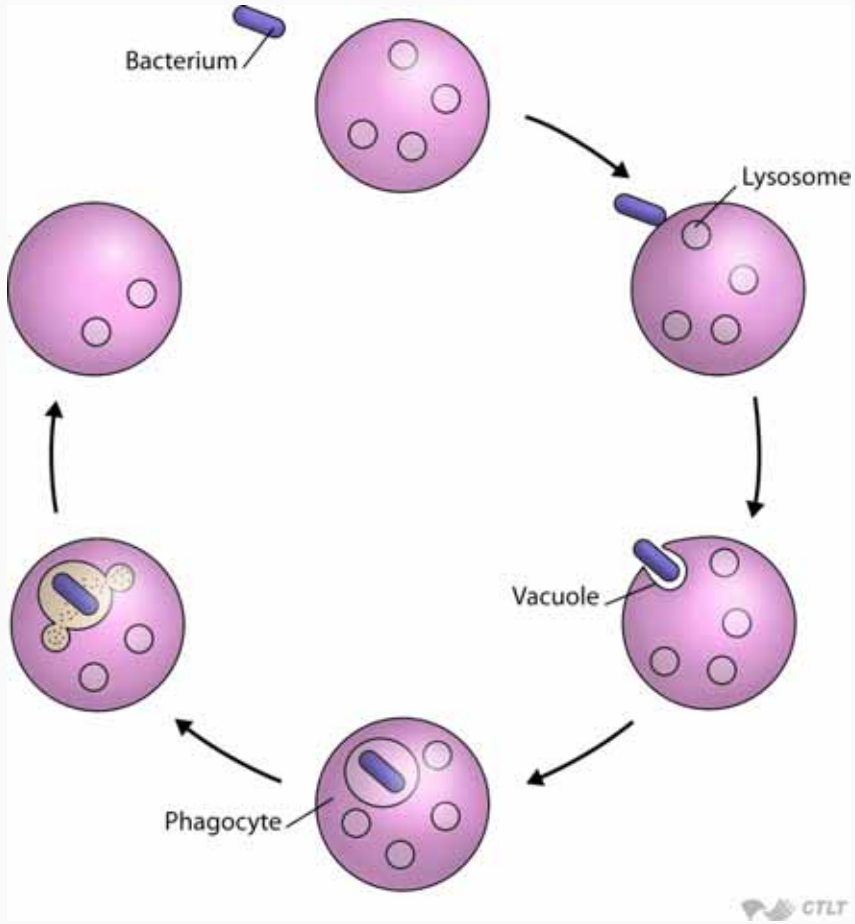
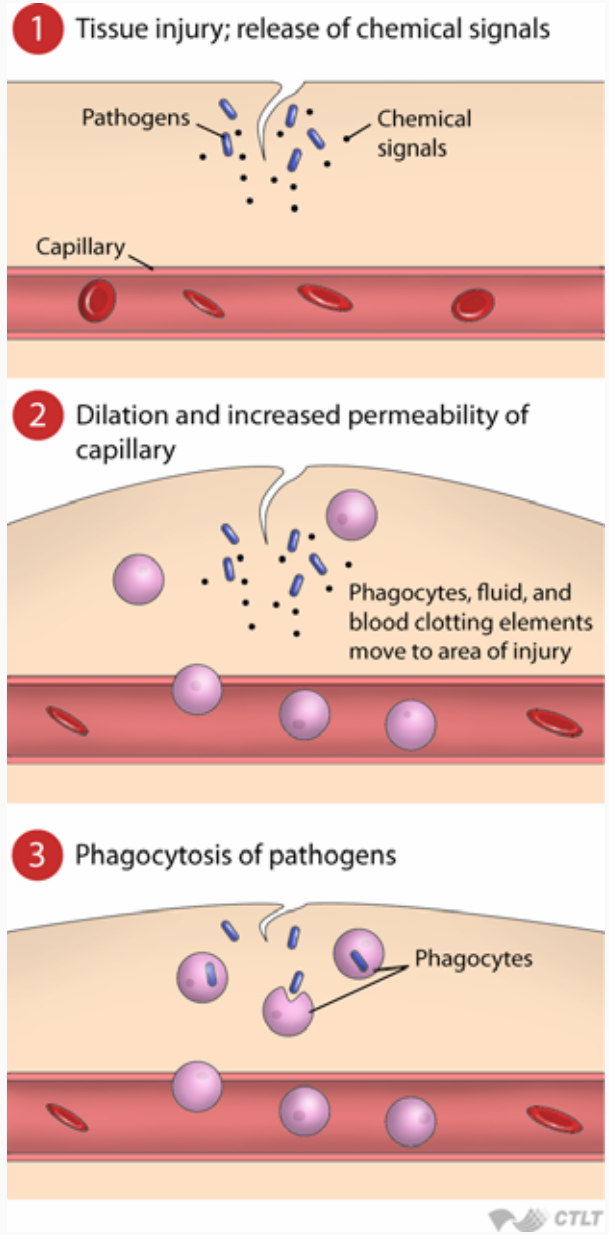


Phagocytosis

- Phagocytes are located in strategic places
  - Skin, blood, gut
- Phagocytes are chemotactic (attracted to sites of injury)
- Phagocytes can be "activated" to become better killers



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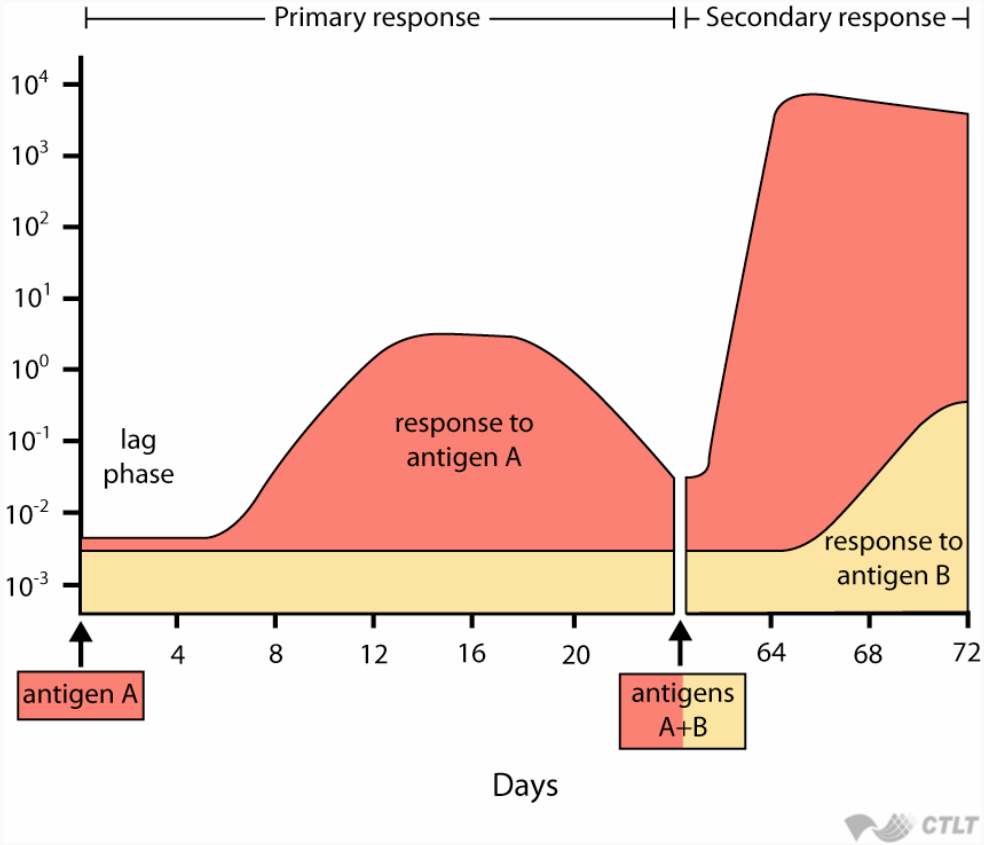
Section B

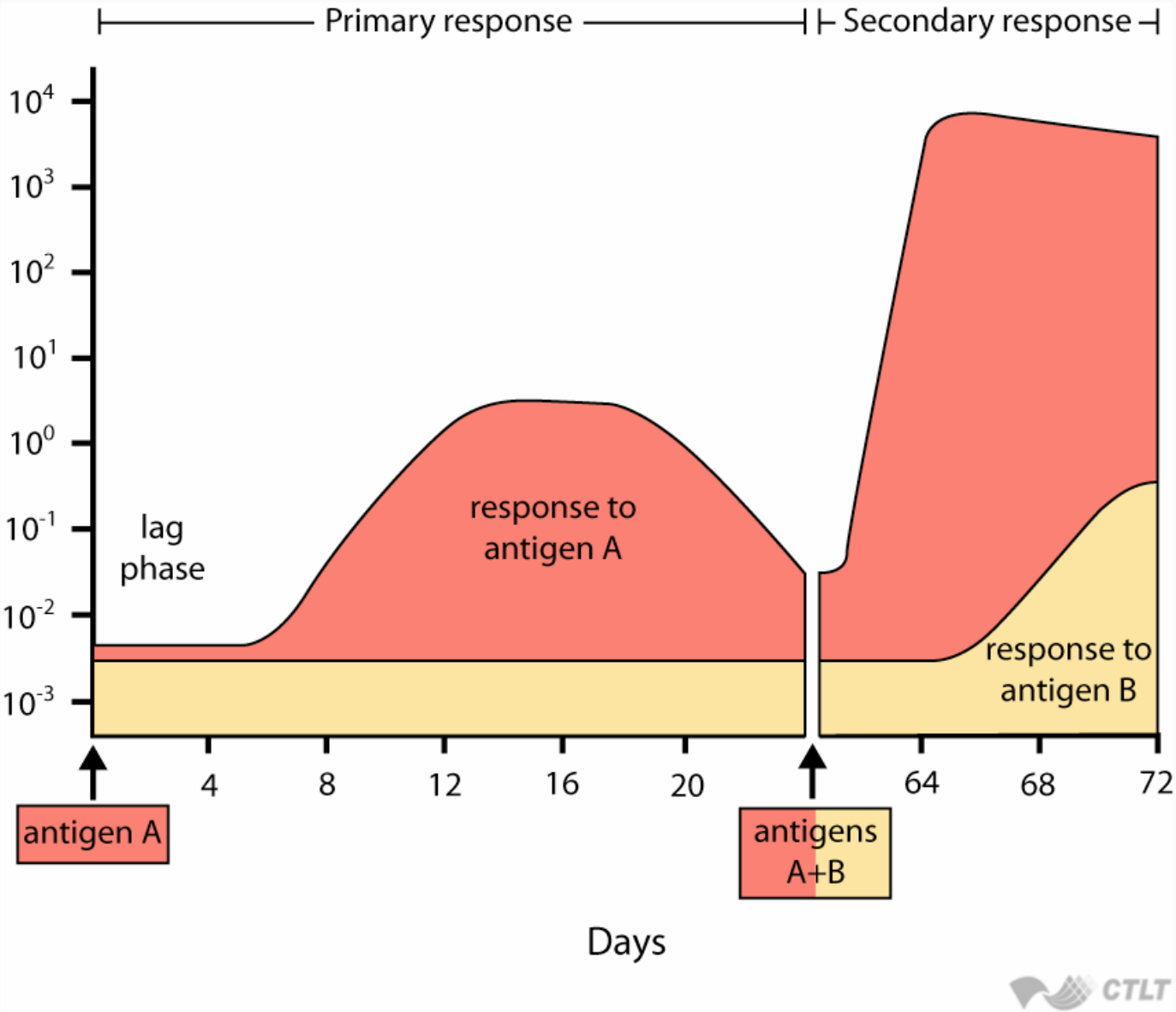
Effector Mechanisms of Adaptive Immunity

Adaptive Immunity

- Arises as a consequence of exposure to a particular target (virus, protein, toxin)
- Specific for that target
- Arises after a delay of a few days
- Potent
- Exhibits "memory"
  - Rapid, large reappearance upon a second exposure



Adaptive Immunity Primary and Secondary Responses



- Humoral: mediated by protein molecules called antibodies
- Cell-mediated immunity (CMI): due to the action of specialized immune system cells

Humoral Immunity

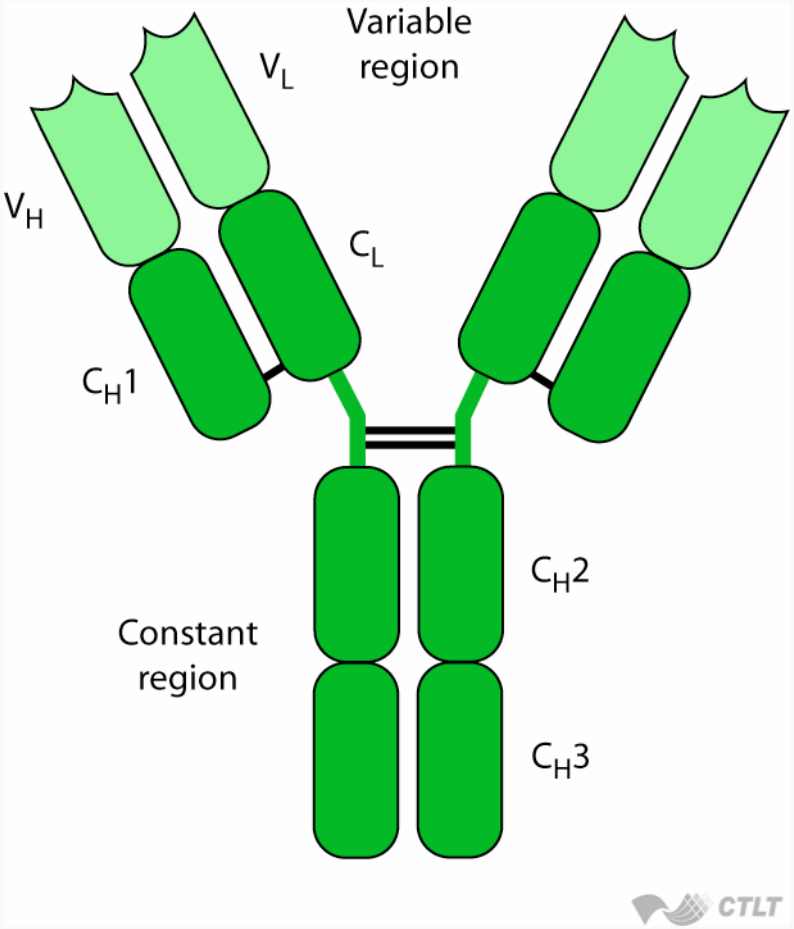
- Mediated mostly by protein molecules called antibodies (Ab), also called immunoglobulin (Ig)
- Antibodies generally are found in extracellular fluids
  - Blood, lymph, mucus
- Antibodies are active against agents with an extracellular phase, including some viruses, toxins, and bacterial infections
  - Not all pathogens have obligatory extracellular phases
    - In some cases, extracellular exposure is brief
    - Antibodies tend to be ineffective against such agents

Antigen Binding by Antibody

- Antibodies act by physically binding to their targets called antigens (Ag)
- Antibody binding to antigen occurs because of a close physical fit between the antibody and the target antigen (epitope)
  - Binding is extremely specific—a given antibody binds only to one (or a few closely related) antigens
- Binding results in inactivation or destruction of the target

Antibody Structure (IgG)

- Four protein chains
  - Two “heavy”
  - Two “light”
  - The heavy chains are identical to each other
  - The light chains are identical to each other
- The chains are held together by disulphide bonds



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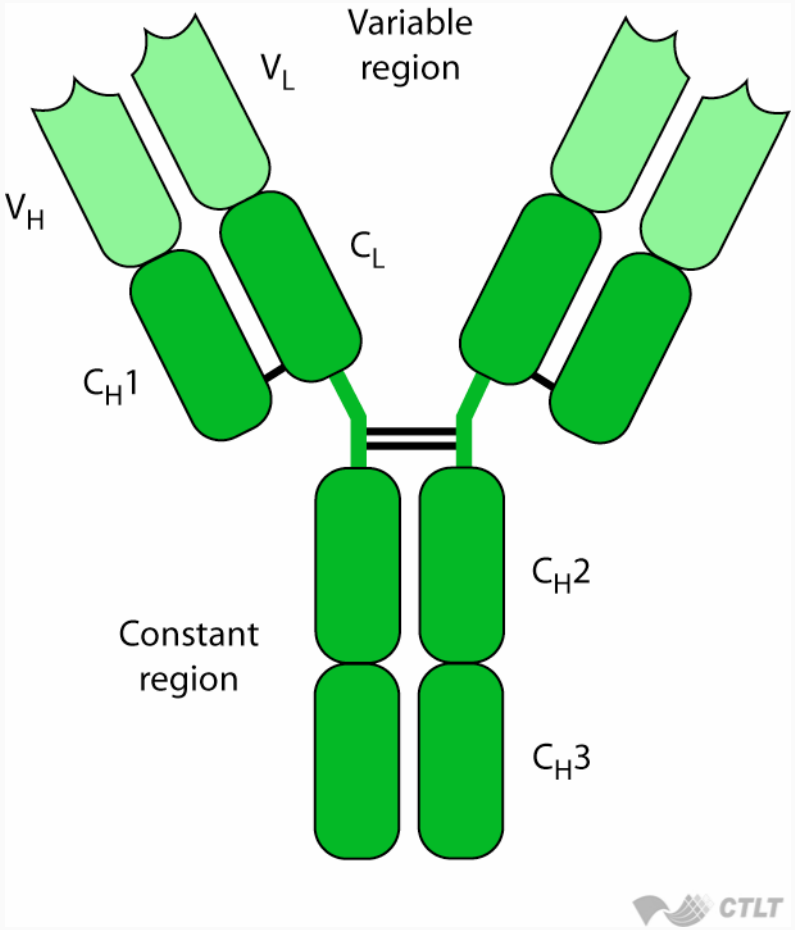
Antibody Structure (IgG)

- Each chain has constant (C) and variable (V) regions
- The variable regions differ among antibody species in amino acid sequence—and therefore shape
- Antibodies bind antigens by the variable regions
- The variation in shape is responsible for differences in specificity of different antibody species



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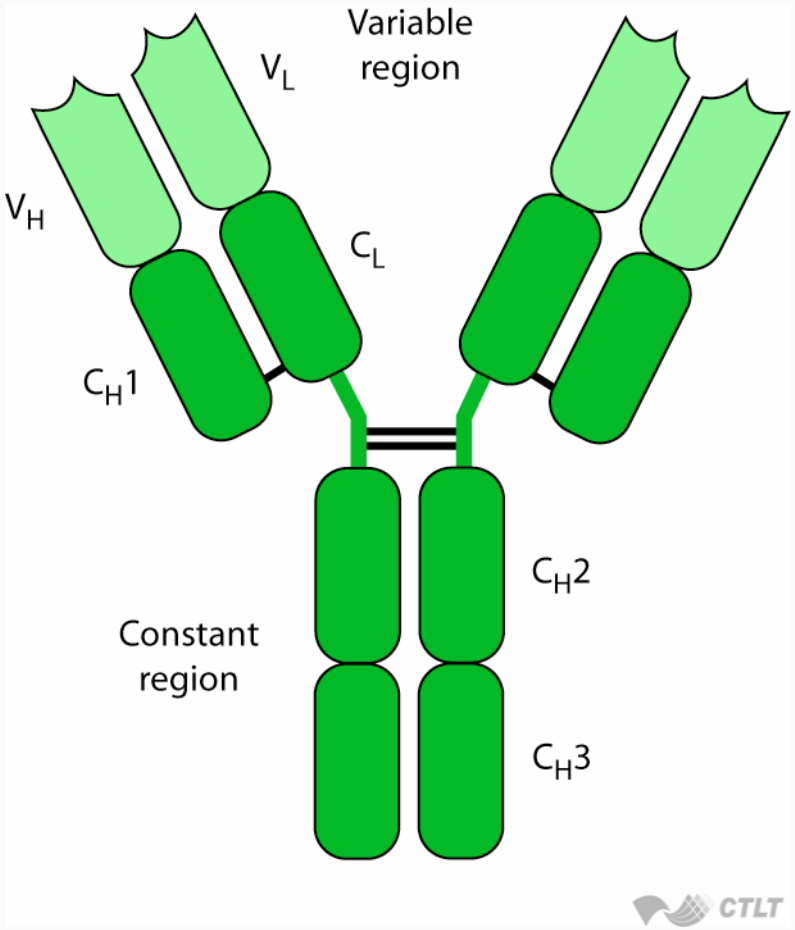
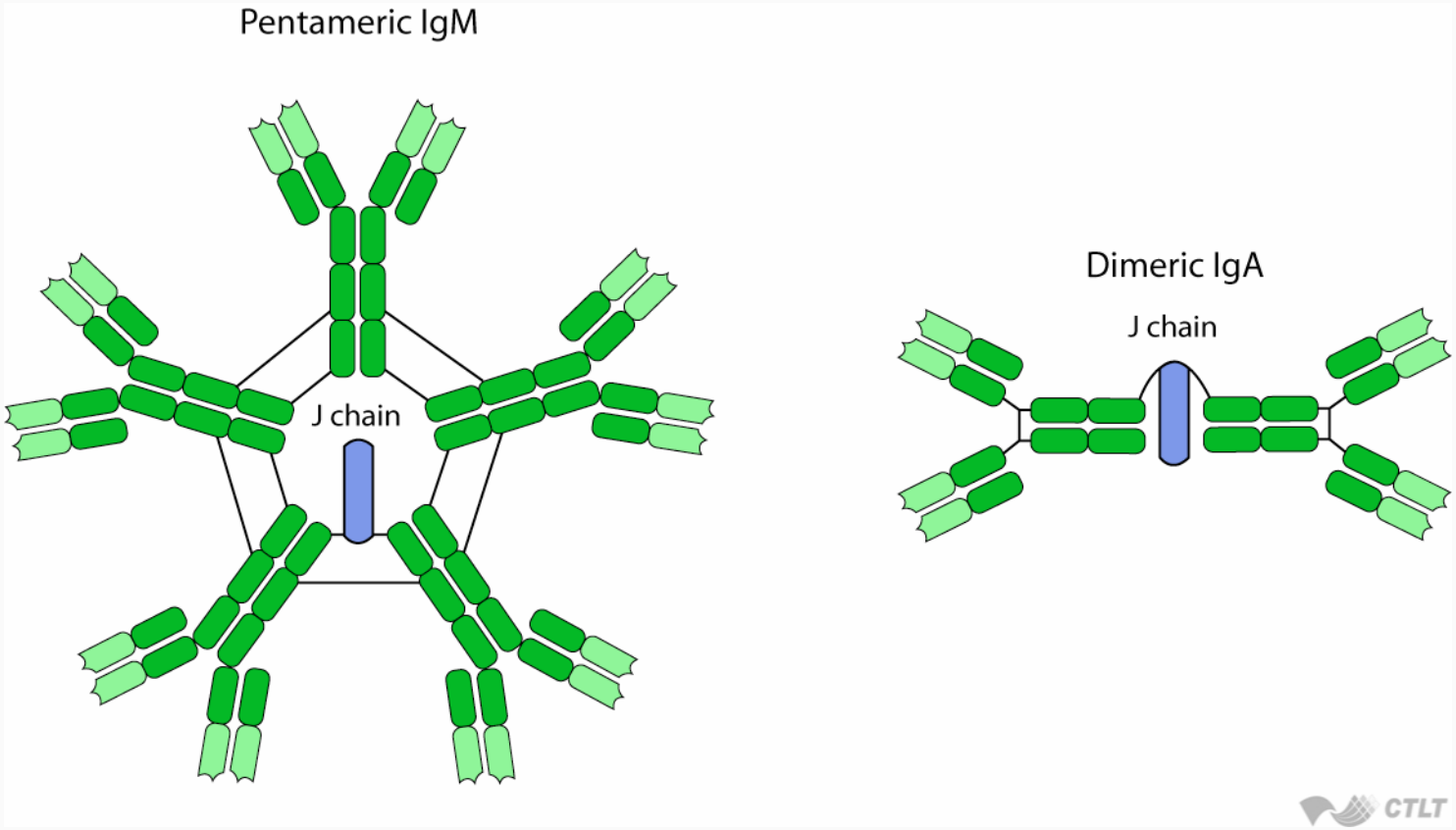
Antibody Structure (IgG)

- It is estimated that there can be about 10^{11} different variable region amino acid sequences, and so about 10^{11} antibody specificities
- At a given time, about 10^{9} are found in an individual
- Antibody diversity is generated by DNA rearrangements that occur during immune development



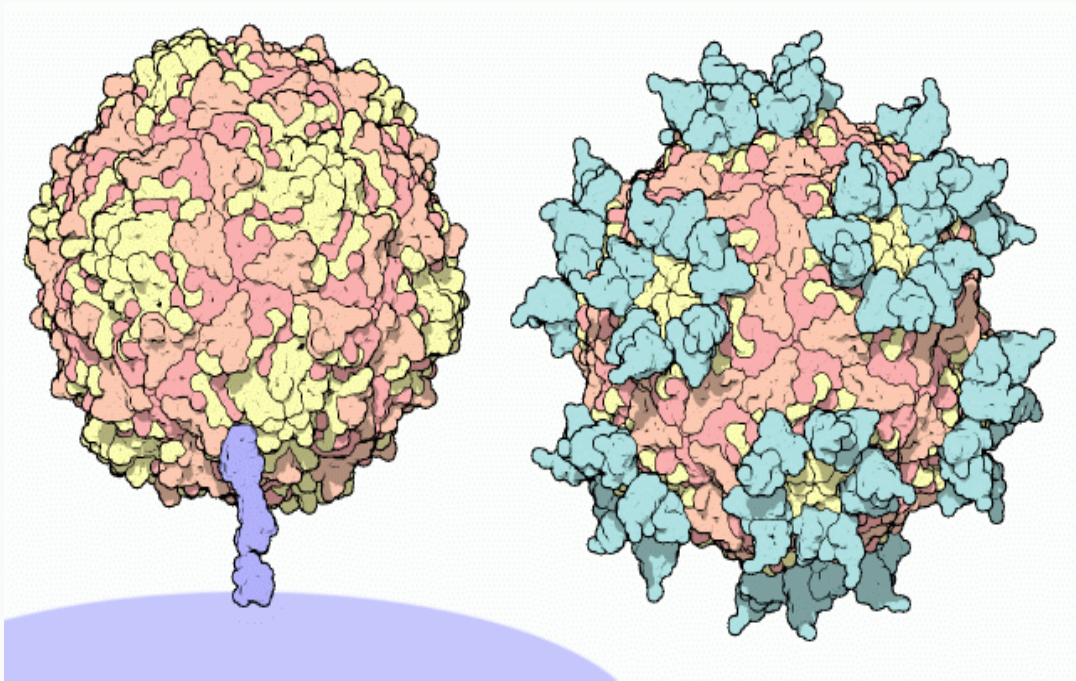
Antibody Structure (IgM, IgA)

- There are several different types of antibody, each with specific functions
  - Two examples are IgM and IgA, which are important antibodies on mucosal surfaces



Neutralization by Antibody

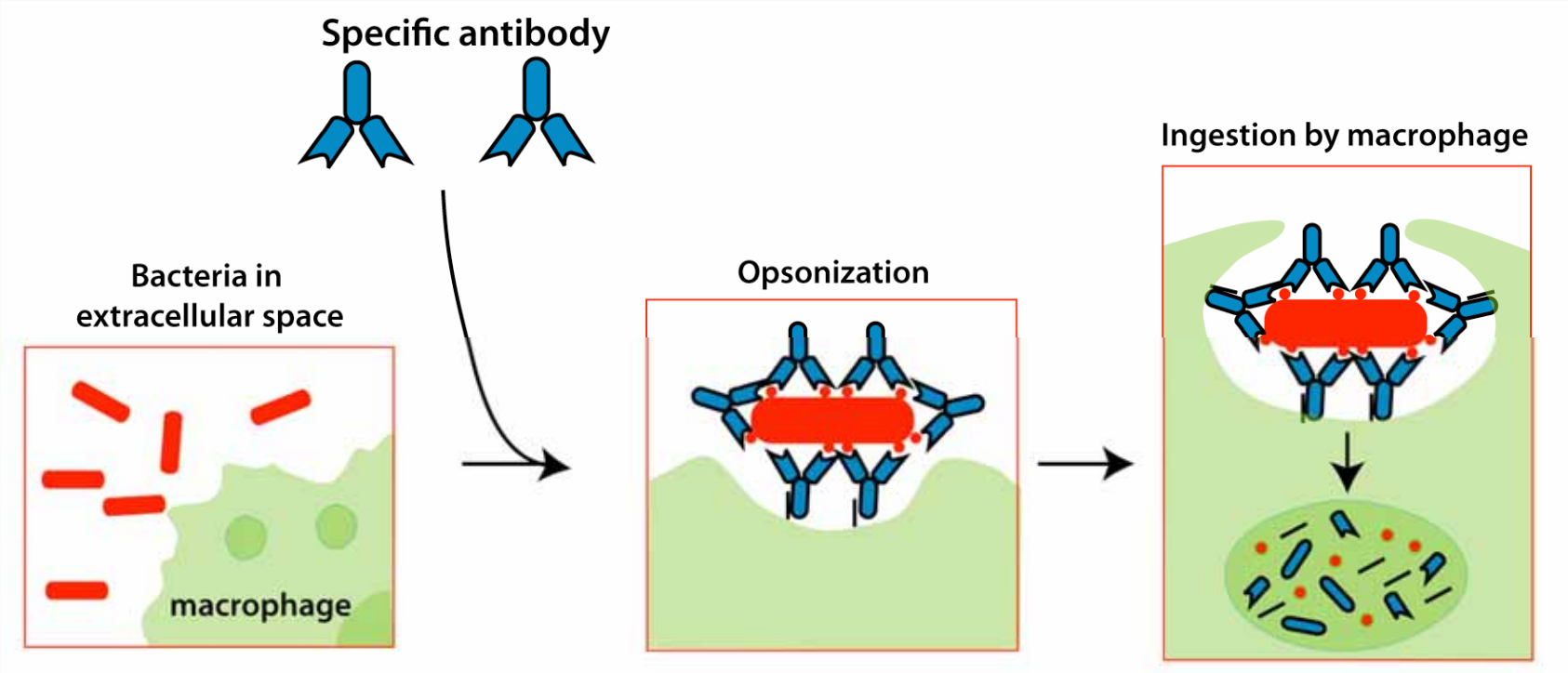
- "Neutralization" occurs when antibody binding to a target interferes directly with function



Human rhinovirus

Opsonization by Antibody

- Phagocytosis can be made much more efficient by antibody



Additional Functions of Antibody

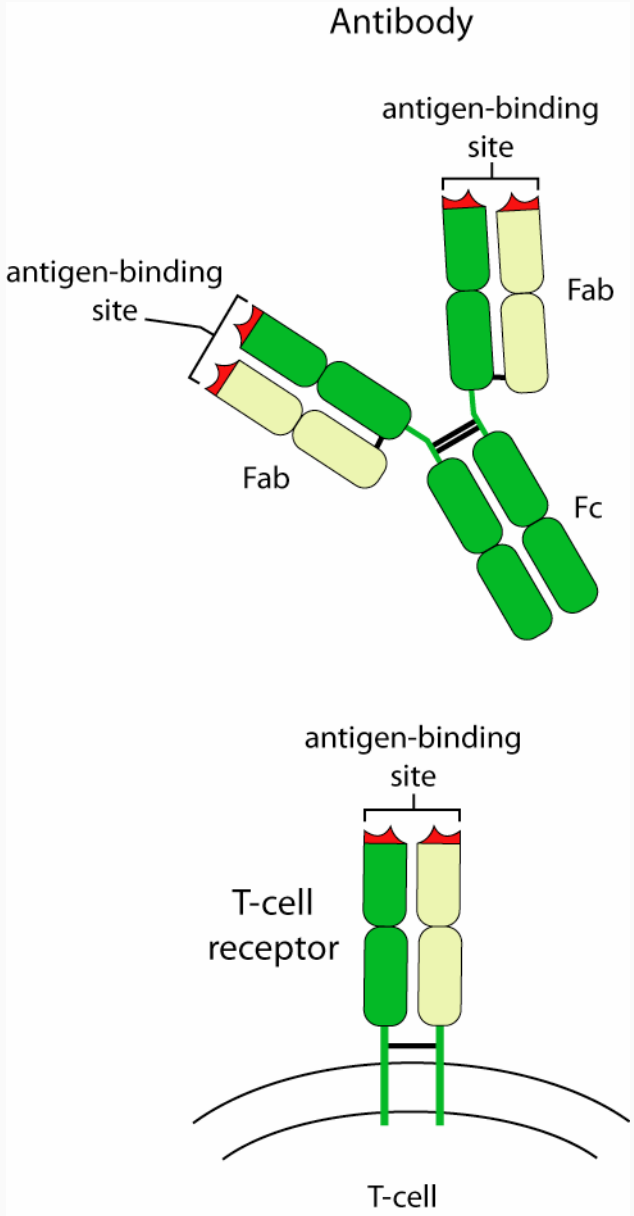
- Complement fixation
- Antibody-dependent cytotoxicity
- Both depend on the binding of Ab to the outside of a cellular target to recruit effectors that kill the cell

Cell-Mediated Immunity (CMI)

- The primary effectors of CMI are cytotoxic T cells (killer T cells, $CD8^+$ T cells, CTLs)
  - Activated macrophages also participate
- Cytotoxic T cells kill other cells
- The primary targets of cytotoxic T cells are usually pathogen-infected cells
- Like humoral immunity, CMI depends on specific recognition of an antigen by a protein: T-cell receptor

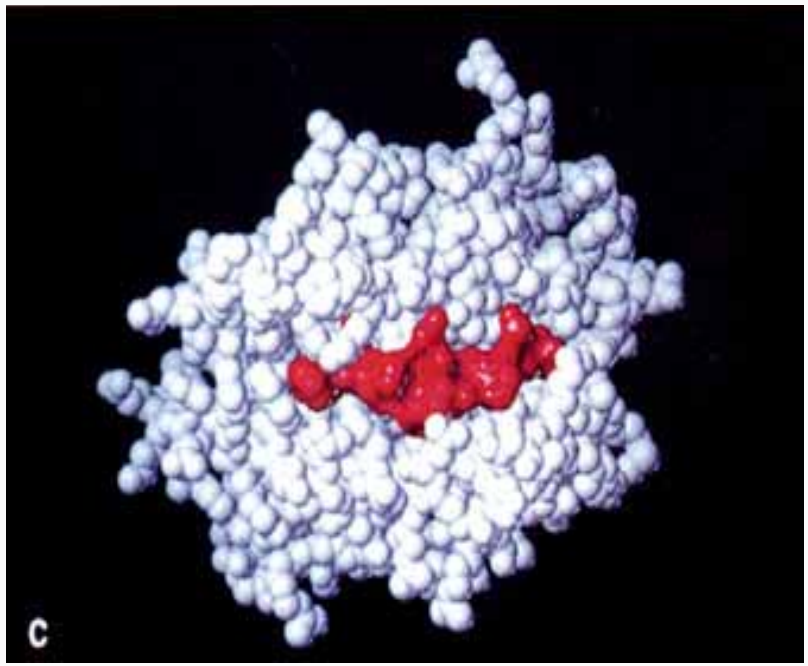
T-Cell Receptor (TcR)

- Primary recognition molecule in CMI
- Similar in structure to antibody
  - Two chains
  - V and C regions
  - Membrane-bound



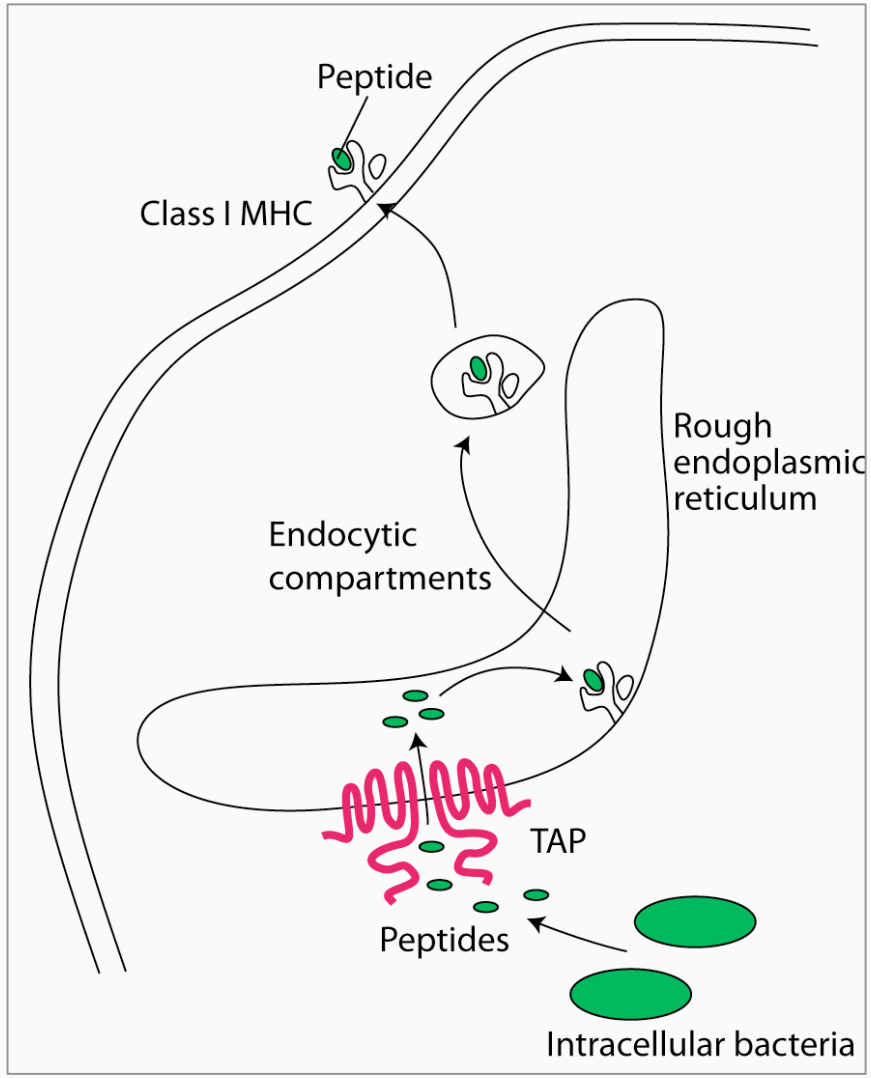
Recognition by TcR

- TcR recognizes antigen by shape
- Recognition is of antigen fragments, bound to another specialized immune system protein, the MHC I antigen
- This is called "presentation"
- MHC I is found on the surface of essentially all cells



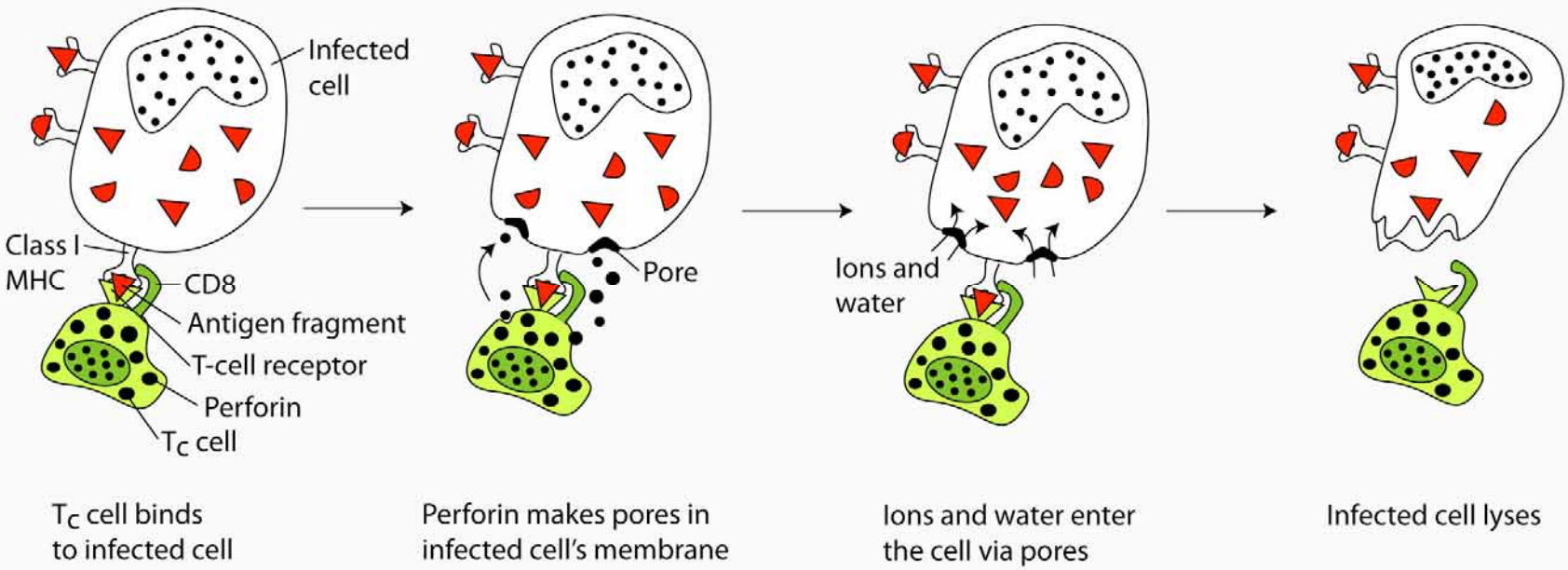
Antigen Presentation

- The targets of CMI tend to be pathogen-infected cells
- Presentation is the consequence of a specific mechanism:
  - Processing
  - Intracellular loading of MHC I
  - Transport to the cell surface



Killing by CMI

- Antigen is presented
- Antigen is recognized by cytotoxic T cell
- The T cell releases pore-forming proteins
- The target cell dies, killing the internal pathogen



Humoral vs. Cell-Mediated Immunity

- Humoral immunity
  - Antibody-mediated
  - Effective in extracellular spaces
- CMI
  - Mediated by T cells
  - Effective against intracellular pathogens
  - Kills infected host cells

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Section C

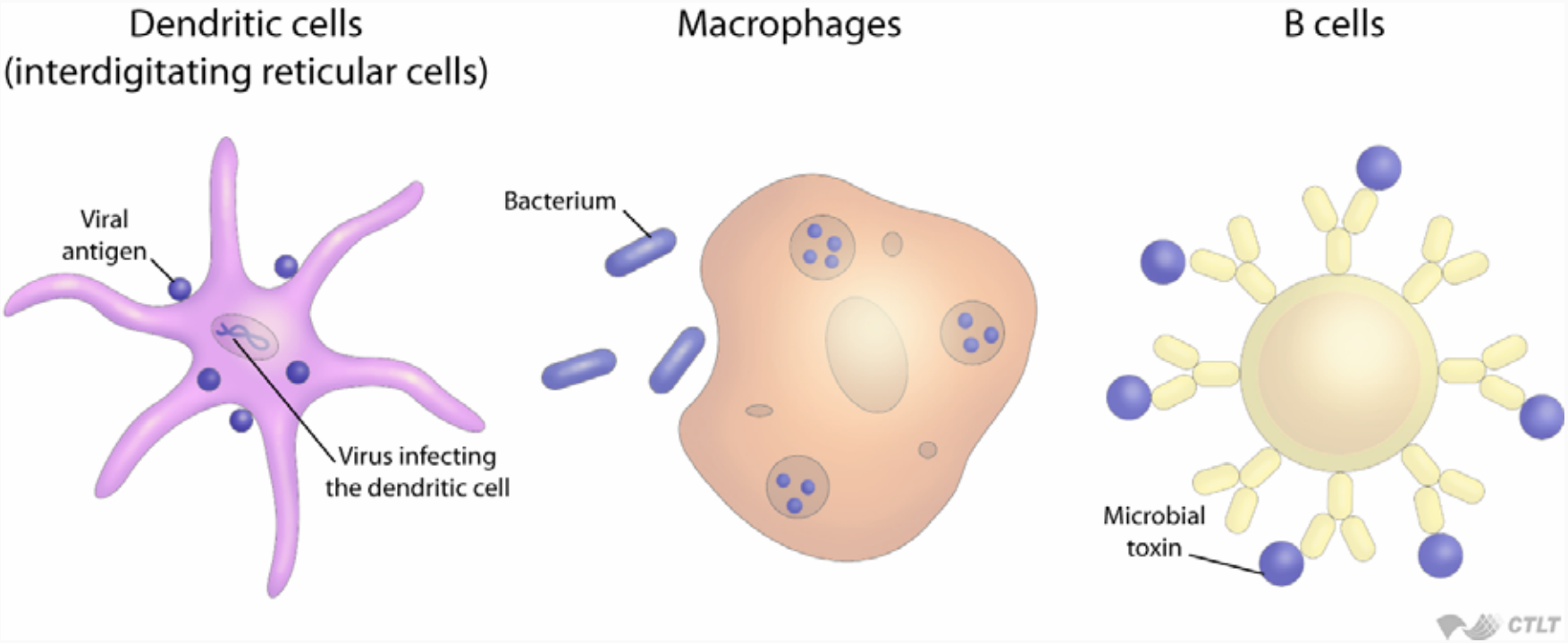
Induction of Adaptive Immunity

Induction of an Immune Response

- Induction of the humoral and CMI responses involve parallel mechanisms:
  - Effectors arise from initially naïve precursor cells (B and T cells)
  - Precursors bear surface receptors with specificities generated at random (Ig, TcR)
  - Naïve precursors differentiate (acquire effector function) because of interaction between antigen and receptors
  - Development begins with an interaction between the pathogen and professional antigen-presenting cells (APCs)

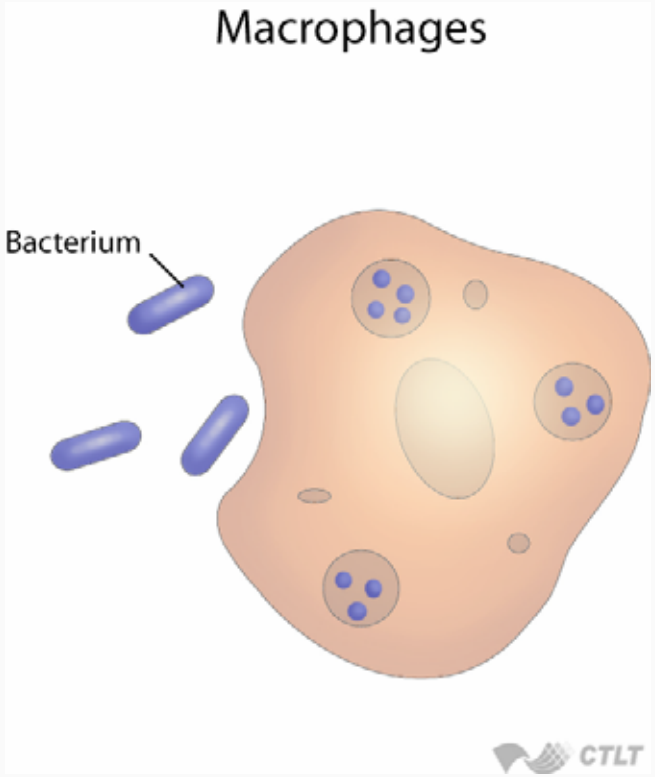
Professional APCs

- Situated for immediate interception of pathogens
- Biologically tuned to effectively initiate a response
- Specialized to deal with different threats



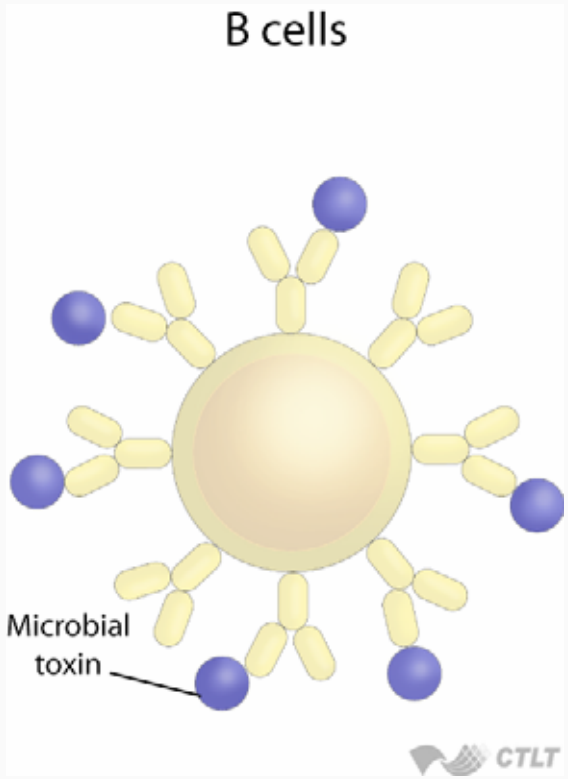
Macrophages

- Stationed in skin, gut, and circulation
- Phagocytic
- Surface receptors are preset to recognize common bacterial cell components
- Engulf, kill, process, and present
- Present using MHC II



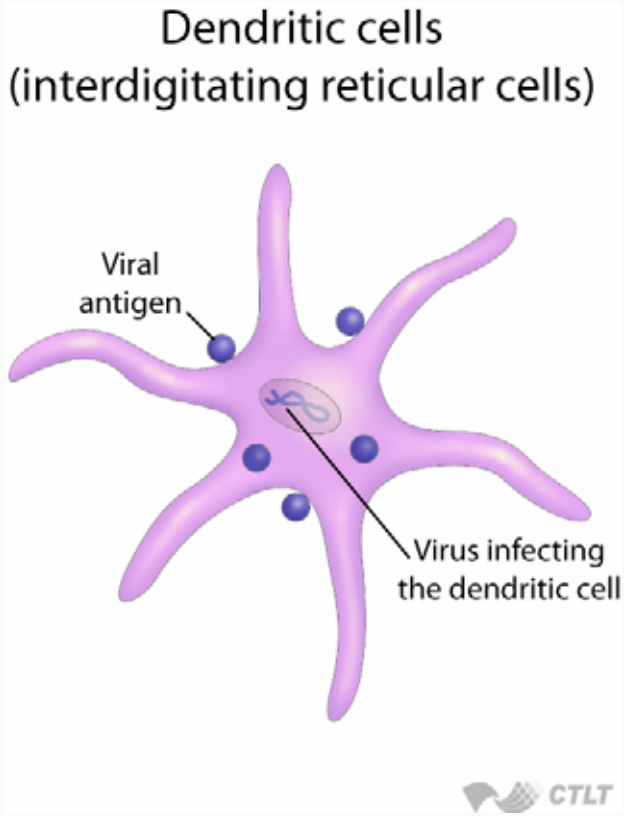
B Cells

- Stationed in lymph nodes and in the circulation
- Surface receptor is membrane-bound antibody
- Antibody specificities are randomly generated
- Antigens binding stimulates phagocytosis
- Antigens are processed and presented on MHC II



Dendritic Cells

- Stationed in skin
- Particularly susceptible to infection by viruses
- Present internally-produced antigens on MHC I



Maturation of T Cells

- T cells are produced as naïve precursors
  - No effector function
  - Random TcR specificities
- Maturation is triggered by encountering a cell presenting a recognizable antigen
- Maturation of T cells involves primarily:
  - Acquisition of effector function
  - Proliferation of cells with specificities that suit the pathogen at hand (clonal expansion)

Maturation of T Cells

- Naïve T cells circulate, sampling the antigens presented on APCs
  - Sampling involves brief physical interaction between the antigen (in the context of MHC) and the T cell TcR
- If the antigen is not recognized, the interaction is short lived, and the T cell moves on

Maturation of T Cells

- If the antigen **is** recognized, binding is tight and long lived
  - Stimulatory signals are exchanged (cytokines)
  - The T cell proliferates
  - Effector mechanisms are developed
  - Memory cells are produced

Cytotoxic T Cells and Helper T Cells

- There are two kinds of T cells:
  - Cytotoxic T cells (T_C or CD8+)
  - Helper T cells (T_H or CD4+)
- These differ in function and therefore develop different effector functions
  - T_C kills virus infected cells and develops cytotoxic mechanisms discussed earlier
  - T_H assists in the immune response (below) and develops ”helper” mechanisms (increased ability to secrete cytokines)

Cytotoxic T Cells and Helper T Cells

- T_H and T_C cells arise similarly—but from different naïve precursors
- Also, T_C development is stimulated by antigen presented on MHC I by dendritic cells
- T_H by antigen presented on MHC II

Maturation of B Cells

- Antibodies are the products of plasma cells, which mature from B cells
- Naïve B cells with random surface antibody specificities circulate, sampling the antigens present
- If an antigen recognized by the naïve B cell is encountered, its bind is internalized, and it is presented on MHC II
  - Modest proliferation also occurs, and partial activation toward the plasma cell state
- The B cell is now primed for differentiation, needing only help from a T_H cell

Maturation of B Cells

- The primed B cell continues to circulate, presenting its processed antigen to passing T cells
  - Since it presents on MHC II, only T_H cells are interested
- When a cognate T_H cell is finally encountered, signals are exchanged (as for T-cell maturation above)
  - Cell proliferation occurs
  - Differentiation to plasma cells and IgG production begins
    - (Refinement of specificity)
  - Memory cells are produced

Secondary Immune Response

- Arises from memory cells
- Arises quickly because the activation steps have occurred and need not be repeated
- Is large because of the increased number of starting cells

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Section D

Poliovirus Pathogenesis: A Review

Poliovirus Pathogenesis: A Review

- Transmission by fecal-oral route via contaminated water
- Primary replication/multiplication is in lymphoid cells (specialized cells of the immune system), especially in the gut
- Virus is shed primarily into the gut and is excreted in the feces
- Some virus also enters the blood and reaches other susceptible cells; these include anterior horn cells (motor neurons), which innervate muscle
- Destruction of these cells can result in paralysis
  - *Disease is not a consequence of an essential step in the virus's life cycle*

Immunology and the Polio Vaccine

- Two polio vaccines were developed with support from the March of Dimes campaign initiated in 1938 and sponsored by President Franklin Roosevelt, a paralytic polio victim
    1. Killed virus (Salk), licensed in 1955
    2. Attenuated live virus (Sabin), licensed in 1962

Continued

Immunology and the Polio Vaccine

- The two vaccines have very different immune consequences
- What immunity is induced by each vaccine?
  - What APCs are initially involved? how do they present antigen?
  - What T cells does each stimulate?
  - What sort of immunity does each ultimately produce?

Continued

- What protection is conferred by each vaccine?
  - Against disease?
  - Against viral replication?
- Does each of these vaccines protect an individual against disease?

Continued

Immunology and the Polio Vaccine

- What practical public health advantages does each vaccine have?
- What is current U.S. polio vaccine policy?