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
Phagocytosis

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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
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

- Primary response
- Secondary response

Days

- Lag phase
- Response to antigen A
- Response to antigen B

Antigen A
Antigens A+B
Adaptive Immunity

- **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

Continued
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.

Continued
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

Pentameric IgM

Dimeric IgA

J chain
“Neutralization” occurs when antibody binding to a target interferes directly with function

Human rhinovirus
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
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
- Primary recognition molecule in CMI
- Similar in structure to antibody
  - Two chains
  - V and C regions
  - Membrane-bound
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.
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
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
- 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
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)
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.
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
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
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
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?
What protection is conferred by each vaccine?
- Against disease?
- Against viral replication?

Does each of these vaccines protect an individual against disease?
Immunology and the Polio Vaccine

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