IMMUNITY TO VIRUSES

- Chapter 19

Immunity to Viruses

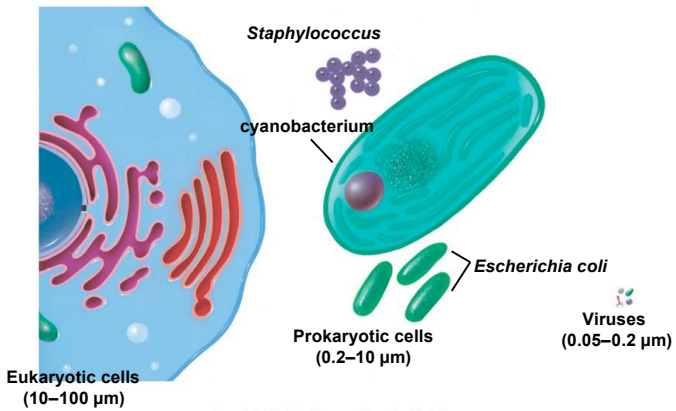
- Basic Aspects of viral infection and disease
- Innate immune control of viral infection
- Acquired immune control of viral infection
- The general structure of a virus
- How a virus replicates
- Effects of viral replication on host cells
- Viral evasion of host immune responses

Basic Aspects of viral infection and disease

- Virus
- Consists of a Molecule of DNA or RNA
  Surrounded by a Protein Coat
  - **The protein coat may be surrounded by a membrane derived from the host cell plasma membrane**
- cannot grow or reproduce without a "Host cell"

  host -specific
  - **Each type is specialized to infect a certain kind of host cell**

The Sizes of Microorganisms



Viral General Info

- Viruses
- come in a variety of shapes
  - **Determined by the nature of the protein coat**
  - **Determined by whether they use host cell plasma membrane**
- Are Host-Specific
  - **Specific bacteria**
  - **Specific cells of multicellular organisms**
  - **Example: HIV infects "helper T cells" of human immune systems**
- Viral Infections Are Difficult to Treat
  - **Mutation rates are high**
  - **Viruses hide within cells**

Basic Aspects of viral infection and disease

- Noncellular and nonliving submicroscopic entities
- Obligate intracellular parasites

- Viral respiratory infections
  - Infants in first year >6 on average
  - Adults usually have 3 to 4 a year
  - Signs and symptoms
    - Fever
    - Increased secretion of fluids
    - Sneezing, coughing
    - Sore throat
    - Malaise
    - Headache
- Gastrointestinal viruses (usually Norwalk viruses)
  - Signs and symptoms
    - Abrupt onset of nausea, cramps, vomiting, and diarrhea

Common Viral Diseases

Table 19.1 Some common diseases caused by viruses in humans

Virus family	Virus	Diseases
Herpesviridae	Herpes simplex virus type 1	Cold sores
	Epstein-Barr virus	Infectious mononucleosis, Burkitt's lymphoma
	Varicella-zoster virus	Chicken pox, shingles
Poxviridae	Variola virus	Smallpox
Hepadnaviridae	Hepatitis B virus	Hepatitis
Papovaviridae	Papillomavirus	Warts
Orthomyxoviridae	Influenza virus	Respiratory diseases
Togaviridae	Rubivirus	Rubella
Paramyxoviridae	Mumps virus	Mumps
	Morbillivirus	Measles
	Respiratory syncytial virus	Respiratory diseases
Rhabdoviridae	Lyssavirus	Rabies
Retroviridae	HIV	AIDS
Coronaviridae	SARS virus	SARS

EMERGENCE OF NEW VIRAL DISEASES

- Mutants, mutants, mutants
- High and rapid rate of viral replication
- Influenza pandemic in 1918/19 KILLED tens of millions of people
- 2003 new form of coronavirus caused severe acute respiratory syndrome (SARS)

- Ability of viruses to
  - infect every type of cell from bacterial to human cells
  - Rapid generation times
  - Large numbers of particles produced
  - High mutation rates
- Can generate new variants in very short periods of time

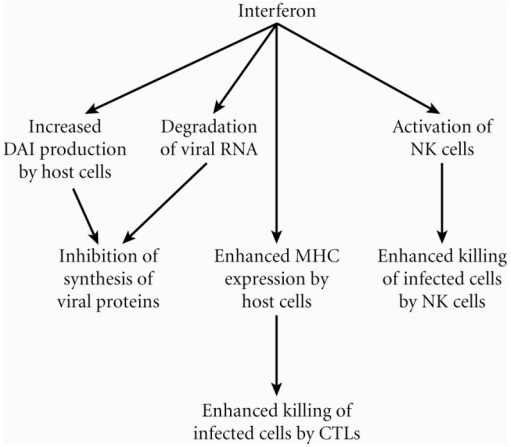
Innate immunity plays a key role in resistance to viral infection

- Viral replication rapidly stimulates innate immunity
- Interferons (IFN) are anitviral factors expressed by many cells when virally infected
- Natural Killer (NK) cells recognize virally infected cells and kill them via cytotoxicity
- Complement proteins MAC can disrupt the viral envelope
  - Phospholipid bilayer stolen from the host cell
- Complement can opsonize viral particles for phagocytosis by Mϕ

Interferons (IFN) have antiviral properties

- Type I and type II IFN
- Unrelated biochemically but both have antiviral effects
- IFN can control viral infections by
  - Binding receptors on infected or uninfected cells
    - prevents further spread of the virus
- IFN binding to IFN-R
  - inhibits synthesis of viral proteins
  - Increase expression of MHC class I molecules
    - Enhances the destruction of infected cells by CTLs
    - prevents uninfected cells from being killed by NK cells
- IFN binding to R on NK cells increases their ability to destroy cells that have decreased MHC class I expression and/or are coated with antiviral antibodies

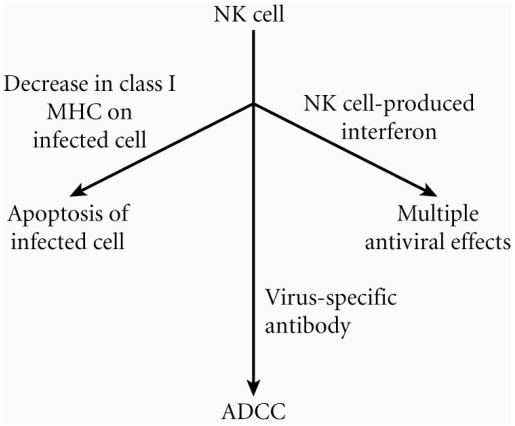
Interferons (IFN) have antiviral properties



Natural Killer (NK) cells can control viral infections

- The virally induced MHC class I downregulation
  - triggers NK cells to kill the infected cells
- Recognize infected cells coated with antiviral antibodies using Fc receptors (FcR)
- and kill them through antibody dependent cell mediated cytotoxicity (ADCC)
- Produce increased amounts of IFN-γ
  - Binds IFN-R to prevent production of virus

Natural Killer (NK) cells can control viral infections



Viruses and Acquired Immunity

- Antibody mediated immunity or humoral immunity
- Cell mediated immunity (CMI)
- Delayed Type Hypersensitivity (DTH) reactions

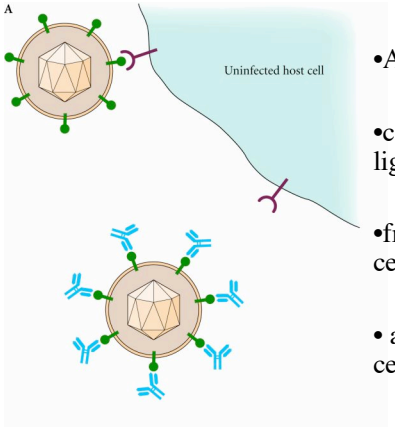
Viruses and Acquired Immunity

- Antibody mediated immunity or humoral immunity
- Antibody mediated antiviral responses
- Antibodies directed at viral surface antigens are the most effective in controlling and clearing viral infections
- Antigens are usually proteins
- Virus can escape antibody binding by mutating the viral antigen gene thereby changing the antigen
  - Influenza virus genes HA and NA are highly variable due to high mutation rate of the encoding genes.
  - HIV rapidly changes the gp160 gene that encodes the gp41 and gp120 surface glycoproteins

Viruses and Acquired Immunity

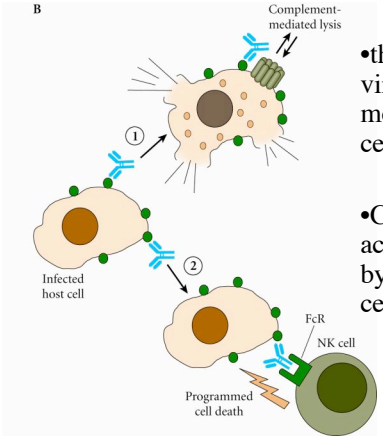
- Antibody dependent control of viruses
  - Example HIV
- Antibodies can prevent a viral ligand from binding to the host cell receptor and entering the host cell
- If a virus succeeds in infecting a cell, the antibody can recognize viral antigens on the membrane of the infected cell.
- Cell is lysed through activation of complement or by ADCC by activating NK cells expressing FcR

Viruses and Acquired Immunity
Antibody dependent control of viruses



- Antibodies (BLUE)
- can prevent a viral ligand (GREEN)
- from binding to the host cell receptor (PURPLE)
- and entering the host cell

Viruses and Acquired Immunity
Antibody dependent control of viruses



- the antibody can recognize viral antigens on the membrane of the infected cell.
- Cell is lysed through activation of complement or by ADCC by activating NK cells expressing FcR

Viruses and Acquired Immunity
Cell dependent control of viruses

- Antiviral Cellular immune responses are
- required to inhibit the further spread of virus in the infected cells and
- are essential for clearing the host of virus once infection has been established
- Effector cells are Cytotoxic T lymphocytes (CTLs)

Viruses and Acquired Immunity
Cell dependent control of viruses

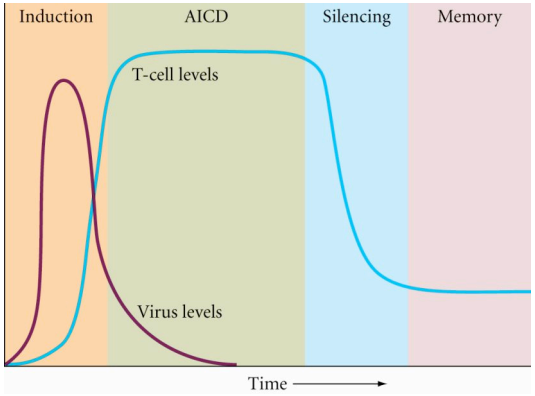
- Effector cells are Cytotoxic T lymphocytes (CTLs)
- Induce cell death 2 ways
  - Perforin/granzyme pathway
  - Fas/ FasL pathway
- Both induce infected cell to apoptose

Viruses and Acquired Immunity
Cell dependent control of viruses

Antiviral CTL responses occur in 4 phases

1. Induction phase
   - CD8+ precursor T cells proliferate, differentiate into effector cells, and attack and kill virally infected cells
2. Activation-induced cell-death (AICD) phase
   - Activated CTLs responding to another encounter with viral antigen undergo apoptosis
3. Silencing phase
   - Loss of AICD but continuation of apoptosis in virus-specific CTLs
4. Memory phase
   - Some of the virus-specific activated CTLs remain viable and stable as memory cells
   - Mostly dormant or resting - but have ability to recognize specific viral antigens, proliferate, and lyse infected cells upon reencounter with the same viral antigen

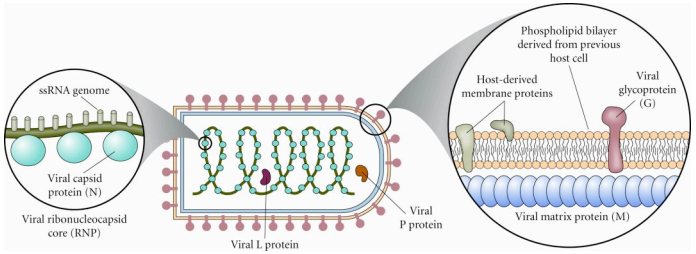
Antiviral CTL responses occur in 4 phases



Structural Properties of the Virus

- Capsid
  - Encloses the genetic material
  - Nucleocapsid is both capsid and genetic material
  - Protective Proteins surrounding the nucleic acid
- Envelope
  - Not all viruses have one
  - Capsid is surrounded by phospholipid bilayer derived from the host cell
  - Allows virus to leave the host cell without damaging it
    - buds off
  - Can be cytoplasmic membrane or nuclear membrane bilayer
  - Host cell proteins are present in envelope making virus appear to be "self"
- Viral nucleic acid
  - DNA or RNA
  - Double or single stranded

Structural Properties of a rhabdovirus



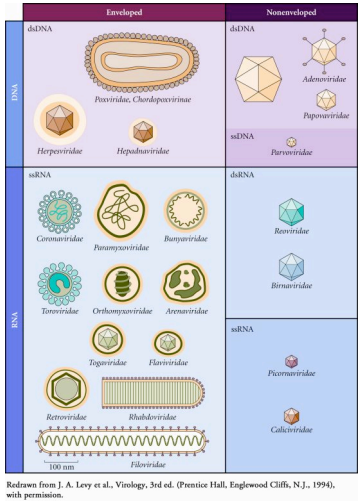
• Enveloped virus

• Negative sense single-stranded RNA and capsid proteins form a helix structure

•L and P are functional enzymes necessary for viral replication

Morphology of Viruses

- Structures of viruses of different families are separated into groups on the basis of
- whether they are enveloped or nonenveloped
- and whether there genome is RNA or DNA,
- double-stranded or single-stranded



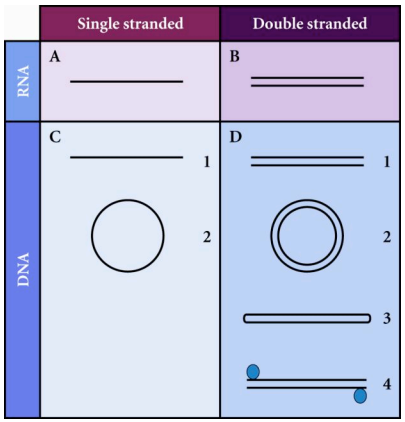
Redrawn from J. A. Levy et al., Virology, 3rd ed. (Prentice Hall, Englewood Cliffs, N.J., 1994), with permission.

Morphology of Viruses

Different forms of viral RNA and DNA

- RNA can be linear
  - Single stranded
  - Double stranded
- DNA can be linear and circular
  - Single stranded
  - Double stranded
- DNA can be linear with covalently linked ends
  - Double stranded
- DNA can be linear with covalently linked terminal proteins
  - Double stranded

Different forms of viral RNA and DNA

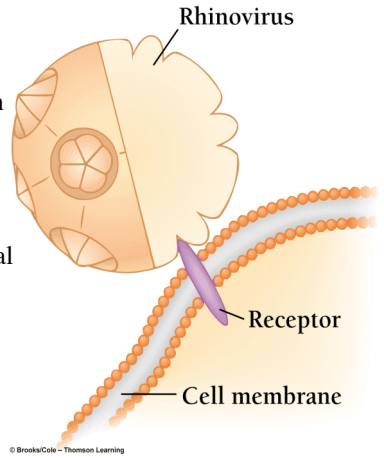


Stages in Viral Life Histories

- Stage 1: The virus attaches to the host cell
- Stage 2: The viral nucleic acid enters the cell
- Stage 3: The cell synthesizes proteins specified by the virus' genes
- Stage 4: The cell replicates the virus' DNA or RNA
- Stage 5: The new viral protein and DNA or RNA assembles into new viruses
- Step 6: The new viruses are released from the cell

Stage 1 = Viral Attachment

- Depends on the interaction between the viral protein and receptor molecules on the host cells membrane
- Basis for specificity of viral infection



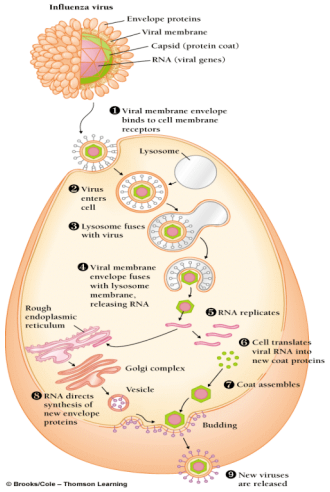
Stage 2 = How Does the Virus Enter?

- Cuts hole in the cell membrane by inducing the cell to engulf the virus particle
- Or by fusing with the cell's membrane
- The virus enters the cell

Stage 3-6 = Manufacturing Virus Particles

- Virus forces the host cell to make viral proteins
- Sometimes destroys host's DNA
- Sometimes through gene regulation
- Most viruses can escape from their host by breaking open the cell membrane (lysis);
- Host cell dies

Viral Life Cycle



Steps of infection by rhabdovirus

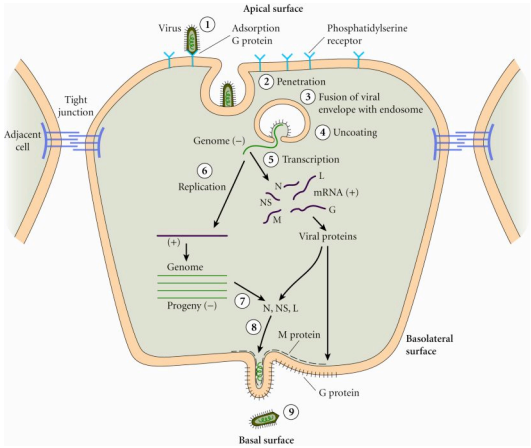


Table 19.2 Host-cell receptors for some human-pathogenic viruses

Virus	Receptor
Lyssavirus	Acetylcholine receptor
HIV	CD4, CCR, CXCR chemokine receptors
Variola virus	Epidermal growth factor receptor
Epstein-Barr virus	CD21
Rhinovirus	CD54
Influenza virus	Glycophorin A receptor

Host cell responses to viral infection

- Cytopathic effects
  - Extensive damage to host cell organelles
- Intracellular inclusions
  - Massive inclusion bodies in the nucleus or cytoplasm of infected cell
  - Clusters of viral particles or products
- Cell fusion
  - Multinucleated giant cell - syncytium
  - Multiple infected cells fuse together
- Host cell metabolic effects
  - Inhibition of host cell's protein synthesis
  - Replicating viral particles comandeer the host cell's transcription and translation machinery

Evasion of Host Antiviral Immune Defenses

- Dormancy/latency and the Proviral state
  - Insert into host genome and remain dormant/latent
    - Papilloma virus, herpes simplex virus,
- Regulation of molecules involved in apoptosis and antigen presentation
  - Escape antibody or complement mediated destruction
    - Viral FcR or CR compete for the real thing
- Disruption of antiviral cytokines
  - Produce viral cytokines that decrease immune response
    - Poxviruses encode soluble IFN-R that bind the IFN and prevent binding to the real thing on NK and CTLs (no IFN-R binding = no activation)
- Viral antigen mutation
  - Antigenic drift
  - Antigenic shift

Evasion of Host Antiviral Immune Defenses

- Viral antigen mutation - example Influenza HA and NA
  - Antigenic drift
    - Random point mutations in HA and NA render them invisible to memory B and T cells
    - Usually results in mild disease since many epitopes will still be the same as the "old" virus
  - Antigenic shift
    - Occurs when segmented RNAs encoding HA and NA are reassorted between different viral strains infecting the same cells
    - This is only possible because the influenza genome consists of 8 separate RNAs
    - Implications for the flu vaccine….
    - All epitopes are essentially "new" and invisible to memory B and T cells
    - leads to severe disease and dissemination