Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 7: Failures of Host Defense Mechanisms

Acquired Immune Deficiency Syndrome (AIDS)

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Understanding Pathogen Infections

- Immune pathway defects lead to opportunistic infections in immunodeficient individuals.
- Opportunistic infections dominate in immunodeficiencies.
- True pathogens can infect those with normal defenses.
- Pathogen strategies are evolved to evade immune detection and destruction using sophisticated methods.
- Fungi and helminthic parasites are not life-threatening in healthy individuals.
- Major infectious agents are viruses, bacteria, and protozoa (AIDS, tuberculosis, malaria) cause significant morbidity and mortality and infect over 100 million people and cause 1-2 million deaths annually.

Immune Evasion by Extracellular Bacterial Pathogens

❖ Strategies of Evasion:

1. **Shielding of surface MAMPs** to avoid detection by pattern recognition receptors on immune cells and destruction by antibody, complement, and antimicrobial peptides.
2. **Modifying the lipid A core of LPS** with carbohydrates and other moieties to interfere with TLR4 binding (Gram-negative pathogens).
3. **Producing variants of lipid A** that act as TLR4 antagonists rather than agonists (Gram-negative pathogens).
4. **Modulating peptidoglycan recognition by NODs** (select Gram-positive pathogens).
5. **Producing hydrolases that degrade peptidoglycan** (select Gram-positive pathogens).

Immune Evasion by Extracellular Bacterial Pathogens
Gram-Negative Pathogens

- **Replication Sites:**
  - Surfaces of barrier tissues (e.g., gastrointestinal or respiratory tract).
  - Tissue spaces or blood post-invasion.
- **Immune Response:**
  - Type 3 immunity (neutrophilic responses, opsonizing/complement-fixing antibodies, antimicrobial peptides).
- **MAMPs:**
  - LPS in outer cell membrane (activates TLR4).
- **Immune Evasion:**
  1. Shielding surface MAMPs to avoid detection.
  2. Modifying lipid A core of LPS with carbohydrates and other moieties to interfere with TLR4 binding.
  3. Producing lipid A variants that act as TLR4 antagonists.

Immune Evasion by Gram-Negative Pathogens

Type III and Type IV Secretion Systems (T3SS and T4SS):

- Specialized needlelike structures (injectisomes) on bacterial surface.
- Inject immune modulatory proteins directly into host cells.

Functions:

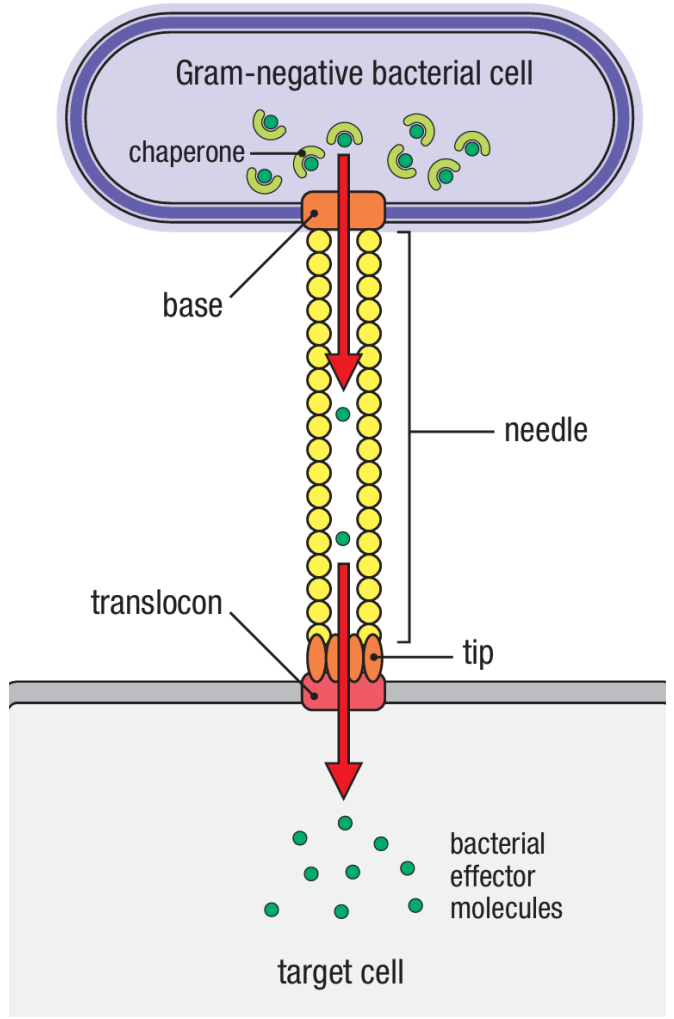
- Deliver bacterial virulence factors to subvert host immune response.
- Block signaling cascades (NFκB and MAP kinases) central to inflammatory response.

Examples:

- **Yersinia outer proteins (Yops):** Produced by Yersinia pestis (bubonic plague).
  - Disrupt actin cytoskeleton essential for phagocytosis.

Significance:

- Essential roles in immune subversion.
- Loss of pathogenicity in mutants lacking these structures.



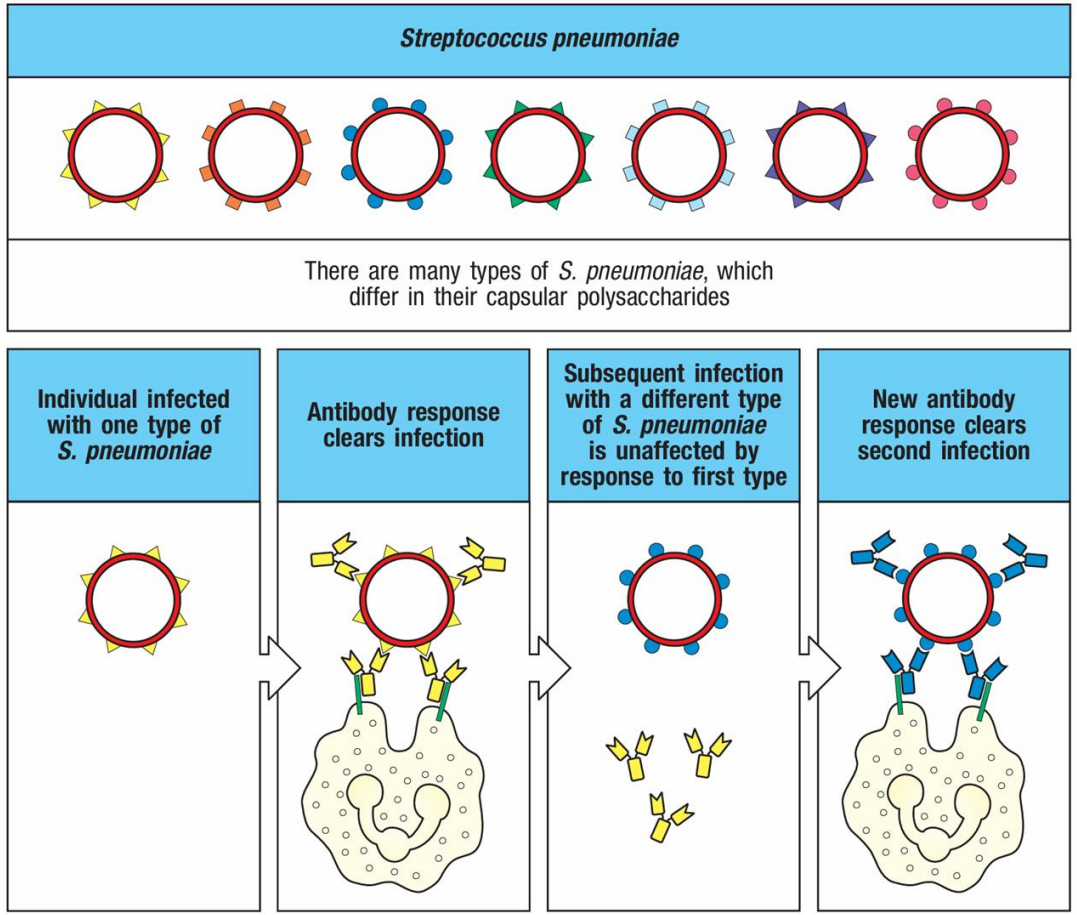
Immune Evasion by Extracellular Bacterial Pathogens
Gram-Positive Pathogens

- **Replication Sites:**
  - Surfaces of barrier tissues (e.g., gastrointestinal or respiratory tract).
  - Tissue spaces or blood post-invasion.
- **Immune Response:**
  - Type 3 immunity (neutrophilic responses, opsonizing/complement-fixing antibodies, antimicrobial peptides).
- **MAMPs:**
  - Peptidoglycans in cell wall (activate TLR2 and NOD1/NOD2).
- **Immune Evasion:**

1. Shielding surface MAMPs to avoid detection.
2. Modulating peptidoglycan recognition by NODs.
3. Producing hydrolases that degrade peptidoglycan.
4. Shielding with a thick carbohydrate capsule.
   - Inhibits recognition of peptidoglycan and complement activation.
   - Prevents antibody and complement deposition.
   - Avoids damage by the membrane-attack complex.
   - Impairs clearance by phagocytes.

Streptococcus pneumoniae and Antigenic Variation

- **Carbohydrate Capsule:**
  - Platform for antigenic variation.
  - Modulates expression of surface antigenic epitopes.
- **Serotypes:**
  - Over 90 known types, distinguished by polysaccharide capsule structures.
  - Identified using specific antibodies in serological tests.
  - Known as serotypes.
- **Type-Specific Immunity:**
  - Infection with one serotype leads to immunity against that type.
  - No cross-protection against different serotypes.
- **Implications:**
  - Each serotype represents a distinct organism to the adaptive immune system.
  - Same pathogen can cause disease multiple times in the same individual.



Antigenic Variation and Immune Evasion by Bacterial Pathogens

- **Antigenic Variation:**

1. DNA rearrangement aids enteropathogenic E. coli and Neisseria species.
2. Fimbriae/pili used for attachment evade antibody-mediated immune clearance.
3. Neisseria pilus gene (pilE) recombines with pilS loci, altering pilus expression.

- **Anti-Immune Strategies:**

1. Inactivating C3 convertase in the complement cascade.
2. Expressing Fc-binding proteins (e.g., Protein A) to block antibody binding.
3. Decorating bacterial surface with host complement inhibitors (e.g., factor H).
4. Defeating antimicrobial peptides (AMPs) like defensins and cathelicidins.
   - Altering membrane composition to reduce AMP binding.
   - Producing proteases to degrade AMPs.

Immune Evasion by Intracellular Bacterial Pathogens

- **Sheltering Within Phagocytes:**

- Avoids extracellular immune effectors (complement and antibodies).

- **Trojan Horse Strategies:**

1. **Blockade of Phagosome-Lysosome Fusion:**
   - Example: Mycobacterium tuberculosis is taken up by macrophages but prevents the fusion of the phagosome with the lysosome, protecting itself from the bactericidal actions of the lysosomal contents.

2. **Escape from Phagosome to Cytosol:**
   - Example: Listeria monocytogenes.

3. **Resistance Within Phagolysosome:**
   - Example: Listeria monocytogenes induces actin filaments for cell-to-cell spread.

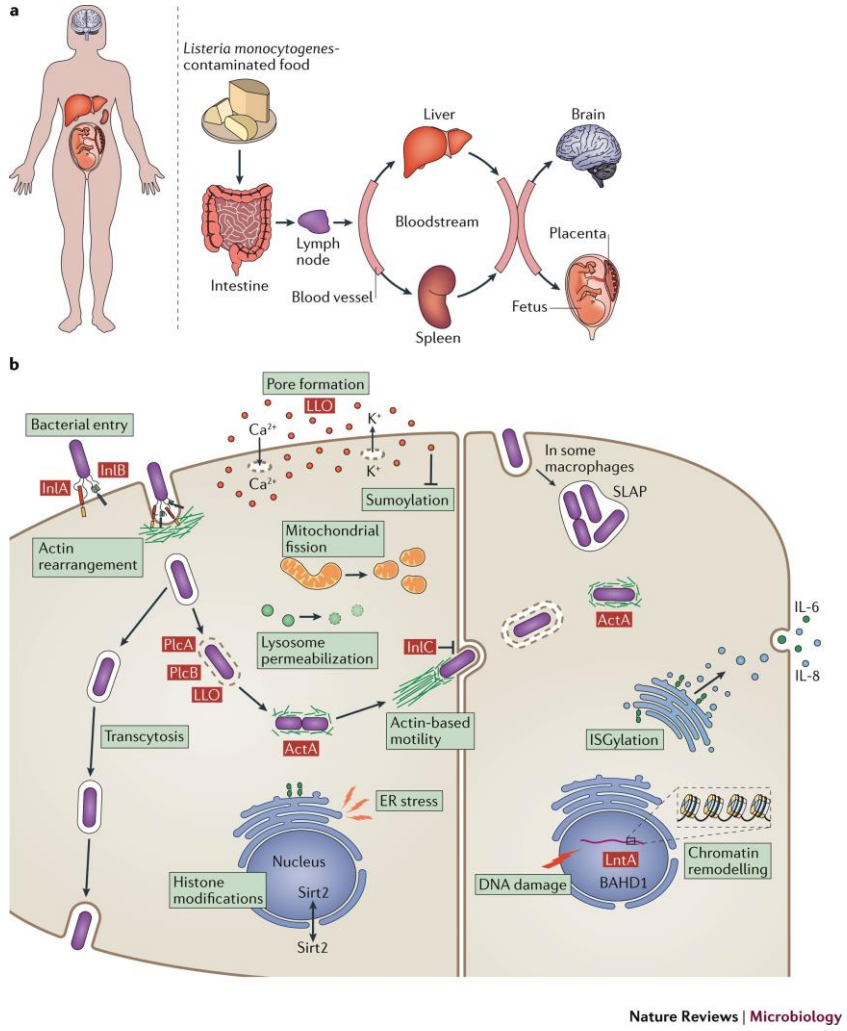
Immune Evasion by Listeria monocytogenes

1.Escape from Phagosome:
- Moves into the cytoplasm of macrophages to multiply.
- Spreads to adjacent cells without entering the extracellular environment.

2.Actin Hijacking:
- Uses cytoskeletal protein actin to form filaments at the rear.
- Actin filaments propel bacteria into vacuolar projections to adjacent cells.
- Vacuoles are lysed, releasing bacteria into the cytoplasm of adjacent cells.

3.Formation of Blebs:
- Induces bacteria-containing blebs on the infected cell surface.
- Blebs express phosphatidylserine on the outer membrane leaflet.
- Mimics apoptotic debris, promoting uptake by phagocytes.

4.Immune Evasion:
- Delivered directly to phagocytic cells, avoiding antibody attack.



Nature Reviews | Microbiology

Immune Evasion by Salmonella Species

Type III Secretion System (T3SS):

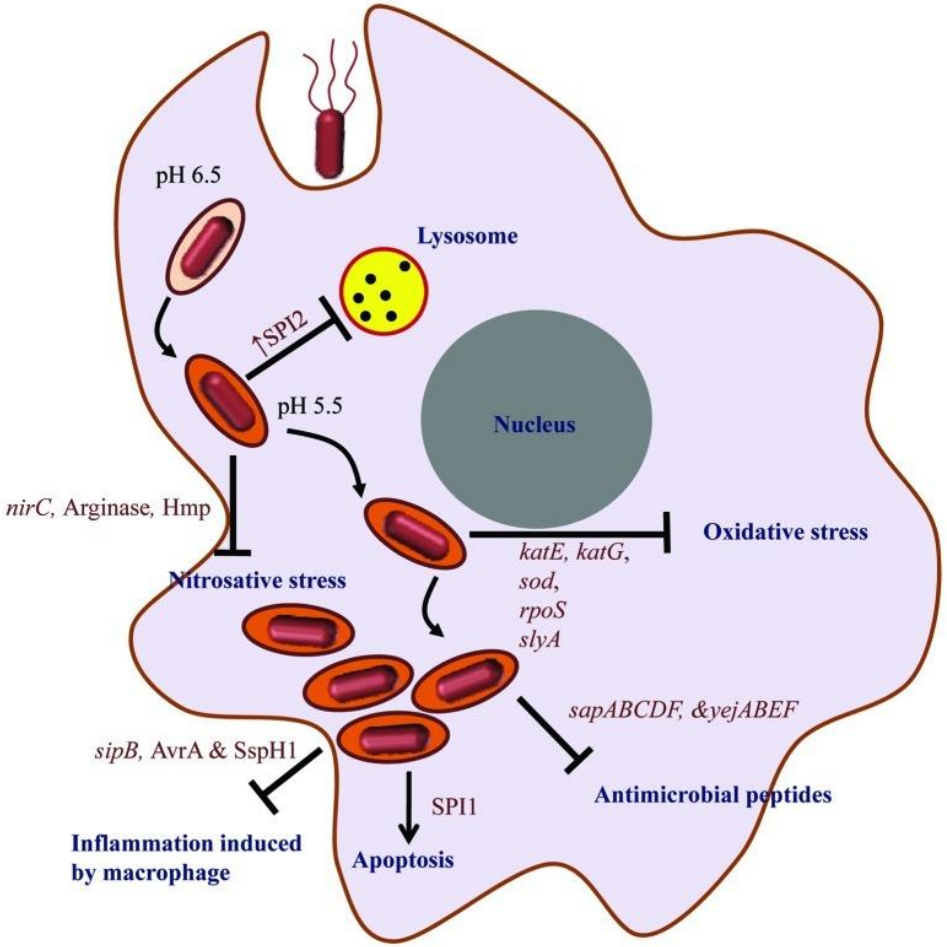
- **Function:** Secretes effectors (e.g., SifA) into host cytosol and membranes.
- **Purpose:** Alters composition of Salmonella-containing vacuole to avoid destruction.

Delaying Macrophage Apoptosis:

- Injects factors that delay apoptotic death of host macrophages.
- Prolongs phagocyte lifespan to deliver bacteria to new hosts.

Counteracting Phagocyte Mechanisms:

- Neutralizes reactive oxygen species.
- Defeats microbicidal peptides in the phagolysosome.

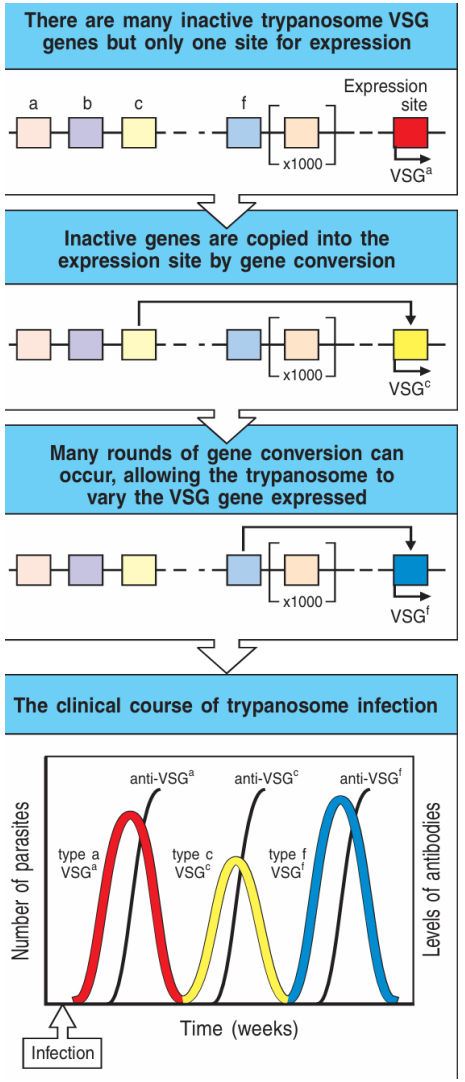


Immune Evasion by Protozoan Parasites

- **Complex Life Cycles:**
  - Partly in humans, partly in an intermediate host (e.g., mosquitoes, flies, ticks).
- **Transmission:**
  - Bypasses normal infection barriers.
  - Infectious agent delivered directly to blood by bite or blood meal.
- **Innate Immune Defense Bypass:**
  - Normal innate immune defenses associated with barrier function are bypassed.
- **Evasion Strategies:**
  1. Complex and varied, leading to 'hide-and-seek' chronic infections.
  2. Characterized by episodic disease manifestations.
- **Key Examples:**
  - **Plasmodium species**: Cause malaria.
  - **Trypanosoma species**: Cause trypanosomiasis (sleeping sickness).

Immune Evasion by Trypanosoma brucei

- **Disease:**
  - Trypanosomiasis (sleeping sickness).
- **Antigenic Variation:**
  - Coated with variant-specific glycoprotein (VSG).
  - Elicits potent antibody response that clears most parasites.
  - Contains ~1000 VSG genes, each with distinct antigenic properties.
  - Only one VSG gene expressed at a time; can be changed by gene rearrangement.
- **Evasion Mechanism:**
  1. Under selective pressure, trypanosomes expressing different VSG escape elimination.
  2. Leads to disease recurrence and cycles of active and quiescent disease.
- **Impact:**
  - Chronic cycles of antigen clearance cause immune complex damage and inflammation.
  - Leads to neurological damage and coma, characteristic of sleeping sickness.
  - Major health problem in Africa.



Immune Evasion by Plasmodium Species

- **Disease:**
  - Malaria, caused by Plasmodium species.
- **Antigen Variation:**
  - Vary their antigens to avoid immune elimination.
- **Escaping Immune Response:**
  - Merozoites burst from hepatocytes and infect red blood cells.
  - Immune system focuses on liver, while parasite escapes to red blood cells.
- **Adaptation to Evade Immune Detection:**
  - **Red Blood Cells:**
    - ✓ Lack MHC class I molecules.
    - ✓ Merozoite antigens escape detection by CD8 T cells.

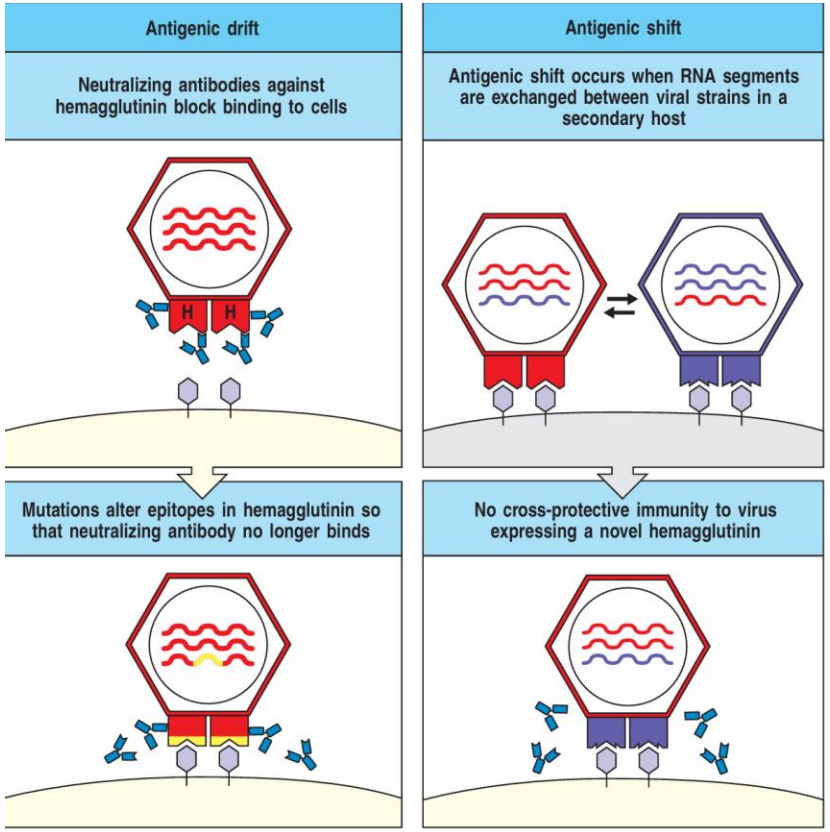
Immune Evasion by RNA Viruses

- **Antigenic Variation:**
  - RNA viruses use mechanisms of antigenic variation to evade adaptive immune responses.
- **Virus Characteristics:**
  - Simplest and most diverse pathogens.
  - Replicate only within living cells, using host cellular machinery.
  - Activate intracellular PRRs, inducing cytolytic immune responses by NK cells and CD8 T cells.
  - Induce type I interferon responses to limit viral replication.
- **Innate Immune Response:**
  - Type I interferons, produced by many cells and especially by plasmacytoid dendritic cells.
  - Early antiviral defense involves NK cells and high levels of type I interferons.
- **Adaptive Immune Response:**
  - Involves all arms of adaptive immunity:
    - ✓ **TH1 Cells:** Help produce opsonizing and complement-fixing virus-specific antibodies.
    - ✓ **CD8 T Cells:** Destroy virally infected cells and produce IFNγ.

Immune Evasion by RNA Viruses

- **General Strategies:**
  - RNA polymerases lack proofreading, leading to high mutation rates.
  - Rapid mutation alters antigenic epitopes, aiding immune evasion.
  - Segmented genomes enable reassortment during replication.

- **Influenza Virus:**
  1. **Antigenic Drift:**
     - Point mutations in hemagglutinin and neuraminidase genes.
     - New variants arise every 2-3 years, causing mild epidemics.
  2. **Antigenic Shift:**
     - Reassortment of segmented RNA genome with animal influenza viruses.
     - Major changes in hemagglutinin result in severe pandemics.



- **Hepatitis C Virus (HCV):**
  - Causes acute and chronic liver infections.
  - High mutation rate in immune epitopes aids evasion.
  - E2 glycoprotein's heavy glycosylation and mutation hinder neutralizing antibodies.
  - Mutation of T-cell epitopes creates escape variants evading cytolytic T-cell responses.
  - HCV factors subvert dendritic cell function, impairing T-cell immunity induction.

Immune Evasion by DNA Viruses

1. **Mechanisms to Subvert NK-Cell and CTL Responses:**

2. **Chronic Infections:**
   - DNA viruses can establish chronic infections.
   - Evolve diverse mechanisms to evade immune defenses.

3. **Low Mutation Rates:**
   - DNA viruses have relatively low mutation rates compared to RNA viruses.
   - Less reliance on antigenic variation.

4. **Large Genomes:**
   - Support larger genomes due to low mutation rates.
   - Accommodate many genes for immune evasion.
   - Example viruses: Poxvirus, adenovirus, herpesviruses (e.g., HSV, EBV, VZV, CMV).

5. **Latency:**
   - Some DNA viruses enter a latent state (e.g., herpesviruses).
     - ✓ Virus not actively replicated.
     - ✓ No viral peptides produced for MHC class I loading.
     - ✓ Avoids detection by cytolytic T cells.
     - ✓ Establishes lifelong infections.

6. **Reactivation:**
   - Latent infections can reactivate, causing recurrent illness.

Evasion Mechanisms of DNA Viruses

- **Evasion of CTLs and NK Cells:**
  - Central to the long-term survival of DNA viruses.
- **Immunoevasins:**
  1. Prevent appearance of viral peptide:MHC class I complexes on infected cell surfaces.
  2. Block peptide entry into the endoplasmic reticulum by targeting TAP transporter.
  3. Prevent peptide:MHC complexes from reaching the cell surface.
  4. Catalyze degradation of newly synthesized MHC class I molecules.
- **Impacts:**
  - Viral factors impair or block presentation of viral peptides to CTLs.
  - Also target the MHC class II processing pathway, affecting CD4 T cells.
  - Viral homologs of MHC class I engage inhibitory receptors on NK cells to block cytolysis.
- **Additional Mechanisms:**
  1. Subvert cytokine and chemokine responses.
  2. Produce viral homologs of cytokines or receptors to inhibit actions.
  3. Inhibit JAK/STAT signaling, cytokine transcription, and transcription factors.
  4. CMV produces cmvIL10 to downregulate proinflammatory cytokines, promoting tolerogenic responses.

Immune Evasion by Epstein-Barr Virus (EBV)

Primary Infection:

- **Initial Acute Infection:**
  - EBV infects B cells by binding to CR2 (CD21) and MHC class II.
  - Causes infectious mononucleosis (glandular fever) in severe cases.
  - Infected B cells proliferate and produce virus, leading to proliferation of antigen-specific T cells.
  - Virus is released from B cells, destroying them.
  - Controlled by virus-specific CD8 cytotoxic T cells.
- **Latency:**
  - **Latent Infection:**
    - ✓ EBV enters latency in memory B lymphocytes.
    - ✓ Virus remains quiescent without replicating.
    - ✓ Limited viral protein expression, including Epstein–Barr nuclear antigen 1 (EBNA1).
    - ✓ EBNA1 prevents its own degradation, maintaining viral genome.
- **Immortal Cell Lines:**
  - **Transformation:**
    - Latently infected B cells can become immortal cell lines in vitro.
    - Can occasionally undergo malignant transformation in vivo (Burkitt's lymphoma).

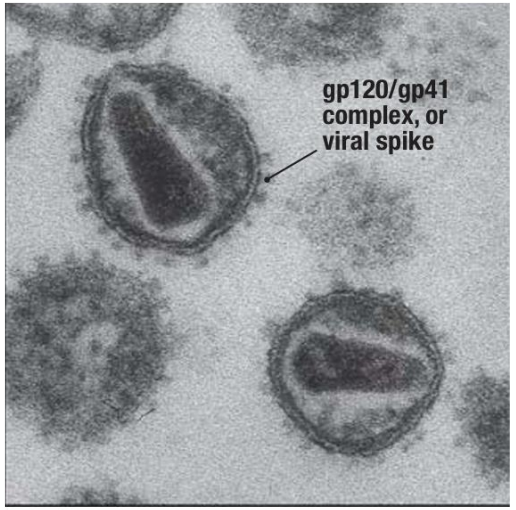
Immune Evasion by Hepatitis Viruses (HBV and HCV)

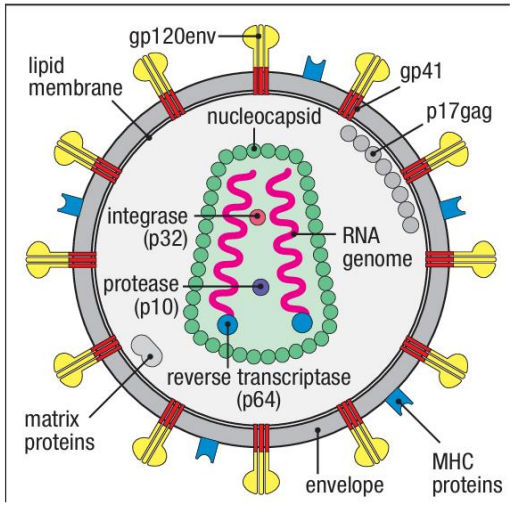
- **Hepatitis B Virus (HBV):**
  - DNA virus causing acute and chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma.
  - Immune responses play a role in viral clearance, but chronic infection often occurs.
- **Hepatitis C Virus (HCV):**
  - RNA virus causing acute and chronic liver infections.
- **Immune Evasion Strategies:**
  - ✓Interferes with dendritic cell activation and maturation.
  - ✓Leads to inadequate activation of CD4 T cells and lack of TH1 differentiation.
  - ✓High mutation rate due to lack of RNA polymerase proofreading, leading to antigenic changes.
- **Chronic Infection:**
- **Consequences:**
  - Inadequate CD4 T cell help leads to chronic infection.
  - Antiviral treatment improves CD4 T cell function and restores cytotoxic CD8 T cell responses.
  - Chronic infection associated with liver cirrhosis and hepatocellular carcinoma.

Acquired Immune Deficiency Syndrome (AIDS) and Human Immunodeficiency Virus (HIV)

Overview:

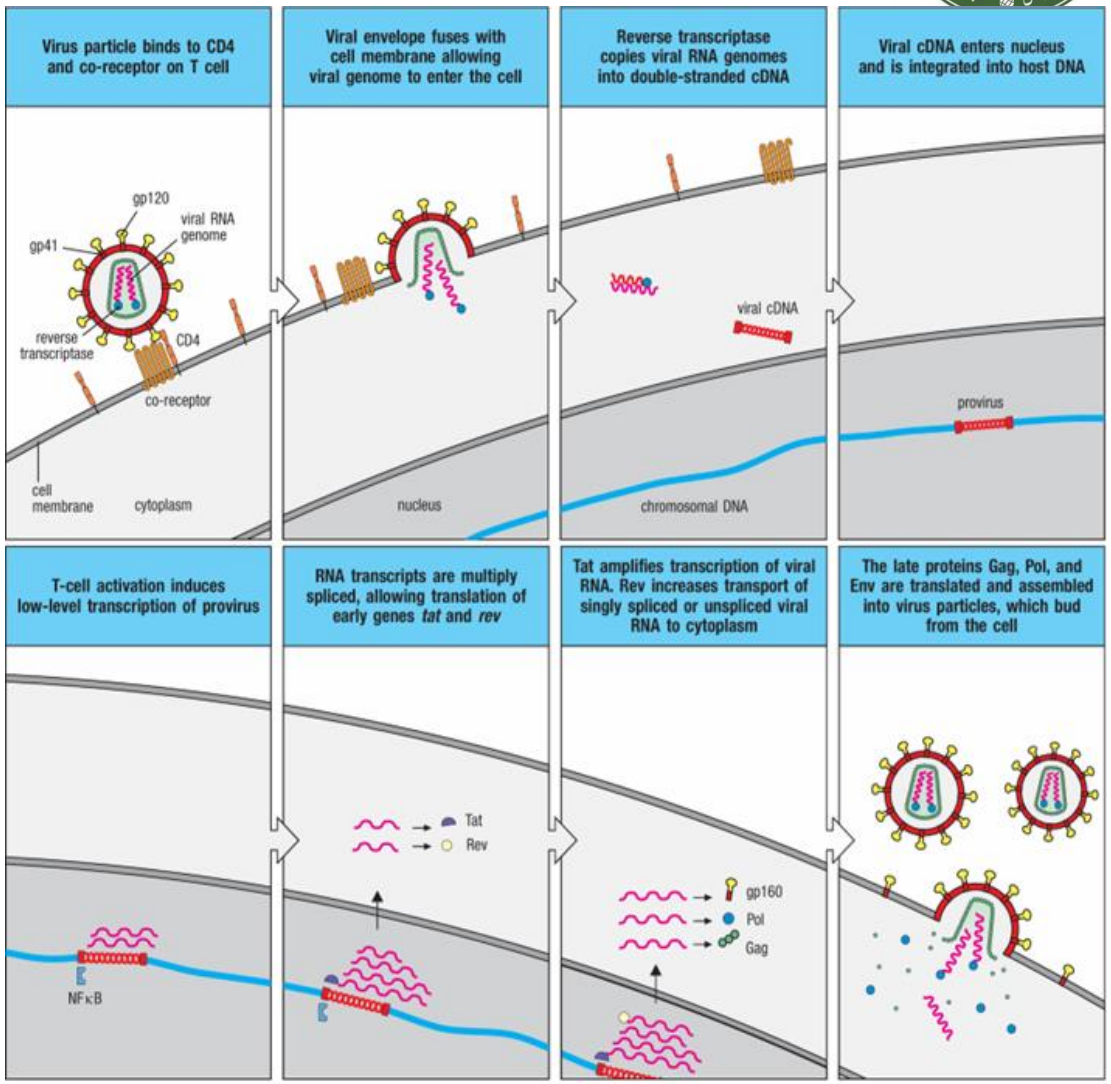
- **Pathogen:** Human Immunodeficiency Virus (HIV)
- **Disease:** Acquired Immune Deficiency Syndrome (AIDS)
- **Characterized by:** Progressive loss of CD4 T cells
- **Consequences:** High susceptibility to opportunistic infections and malignancies
- **Types of HIV:**
  - **HIV-1:**
    - Higher viral loads in blood
    - More easily transmitted
    - High rate of mother-to-child transmission
    - More rapid progression to AIDS
    - Most prevalent cause of AIDS worldwide
  - **HIV-2:**
    - Less prevalent
    - Endemic to West Africa





HIV Infection and Replication in Immune System Cells

- **Primary Targets:**
  1. **CD4 T cells**
  2. **Macrophages**
  3. **Dendritic cells**
- **Cellular Tropism:**
  - Determined by specific receptors on cell surface.
- **Viral Glycoproteins:**
  - **gp120** and **gp41** form trimers in the viral envelope.
  - **gp120** binds to **CD4** and a coreceptor (**CCR5** or **CXCR4**).
- **Coreceptors:**
  - **CCR5: Expressed on effector memory CD4 T cells, dendritic cells, macrophages.**
  - **CXCR4: Expressed on naive and central memory CD4 T cells**
- **Entry Mechanism:**
  - **gp120** binds **CD4** and coreceptor, causing conformational change.
  - **gp41** inserts fusion peptide into host cell membrane, inducing fusion.
  - Viral nucleocapsid enters host cell cytoplasm.



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