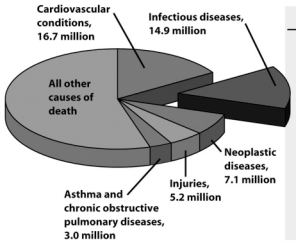
Immune Response to Infectious Diseases Lecture 21 April 12 and Lecture 22 April 17

Robert Beatty
MCB150

Global Burden of Infectious Disease



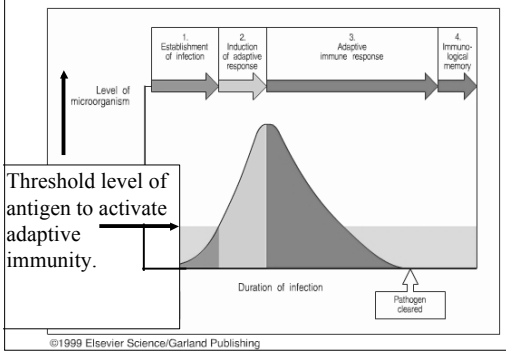
Infectious diseases	Annual deaths
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrheal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

Figure 18-1
Kuby IMMUNOLOGY, Sixth Edition

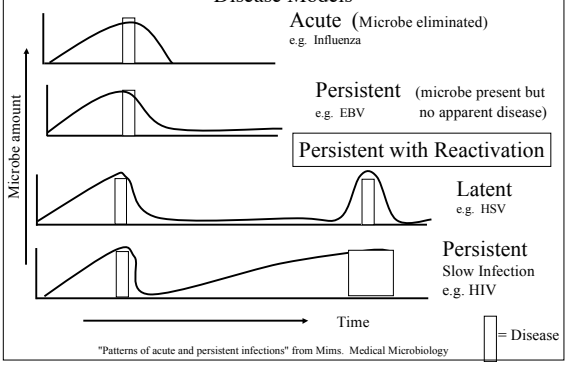
Infection versus disease
Immuncompetent vs Immunocompromised Hosts

- **Primary pathogens** are capable of causing overt disease in healthy (immunocompetent) hosts.
- **Opportunistic pathogens** primarily cause disease in immunocompromised hosts.

Typical Course of Acute Infection



Acute vs persistent infection



"Patterns of acute and persistent infections" from Mims. Medical Microbiology

Obligatory steps for infectious microorganisms

1. Entry into body
2. Spread and replication (localized or systemic)
3. Evasion of host immune defenses
4. Shedding from body for transmission
5. Cause damage in the host (not required)

Pathologic effects of Infection: What causes disease?

Direct effects of pathogens:

- Lysis of cells during infectious process (viruses, intracellular bacteria and protozoan)
- Worms blocking blood vessels
- Toxins

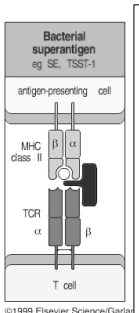
What causes disease?

Exotoxins

- Exotoxins are produced and secreted by extracellular bacteria
  - Exotoxins have a wide range of effects from paralysis to immune activation.
- Exotoxins as Superantigens
  - Non-specifically activate T cells and cause systemic inflammation which distracts adaptive immune response.

What causes disease?

Exotoxins as Superantigens

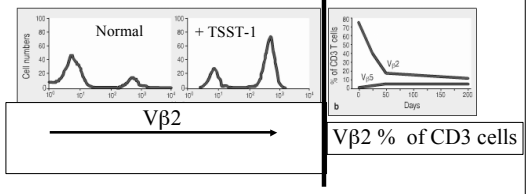


Staphylococcal bacteria secrete Staphylococcal entertoxin B (SEB) to non-specifcally activate T cells.

This is a mechanism of immune evasion.

Toxic Shock Syndrome Toxin-1 (TSST-1)

Staphylococcal bacteria express TSST-1 which activates Vβ2 expressing T cells.



Vβ2

Vβ2 % of CD3 cells

What causes disease?

Endotoxins

- Endotoxins are integral parts of microbial cell wall that activate inflammatory response.
  - Example: LPS on gram-negative bacteria can act as B cell mitogen.
- Systemic bacterial infection with endotoxins can activate acute phase response.

Pathologic effects of Infection: What causes disease?

Host Immune Response

- Tissue damage from inflammation or killing of infected cells is necessary to kill off invading pathogens.

BUT

Immunopathology is often the result.

What causes disease?

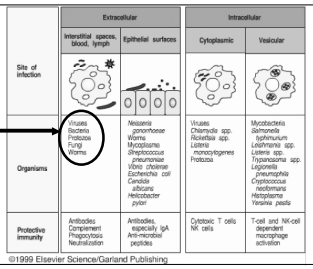
Adaptive immune responses

- Antibody mediated: Activate inflammation, C', ADCC, immune complex disease.
- Cell mediated: Chronic activation of cell mediated immune responses can result in granuloma formation.

Where a pathogen is located influences what type of immune response will be activated.
Location, Location, Location

Extracellular vs Intracellular

At some point all pathogens are outside cells.



Host responses to different pathogens

- Extracellular bacteria usually live in mucosal tissue, or blood.
- Intracellular bacteria and parasites live in endosome or cytoplasm.
- Viruses are intracellular pathogens take over host cell machinery for replication.
- Extracellular parasites can be Protozoa that live in blood or mucosal or helminths (worms) which live throughout body.

What determines the type of host immune response?

Location, Location, Location

- Different innate immunity mechanisms based on location.
- For adaptive immunity it is important to effectively mobilize correct immune defense.
  - Antigen processing can determine CD4 vs CD8
    Th1 vs Th2
    Cell Mediated vs Antibody

Innate mechanisms of defense

Physical Barriers
- Skin
- Mucosal surfaces

Complement
- Alternative and MBL pathways

Cells
- Macrophages
- Neutrophils (mast cells, eosinophils)

Physical barriers to infection

Skin

Epithelial tight junctions form a seal against the outer environment and prevent most pathogens from gaining access to the body

Mucosal surfaces

- Lungs have mucus flow driven by cilia on lung epithelial cells helps expel inhaled pathogens
  - Secretion of surfactant proteins (SP-A and SP-D) that bind pathogens and aid phagocytic uptake
  - Antimicrobial peptides
- Intestinal lining has low pH, digestive enzymes, and antimicrobial peptides make for an inhospitable environment
  - Commensal bacteria in the gut prevent colonization by pathogens

Commensal bacteria can prevent infection by pathogenic bacteria

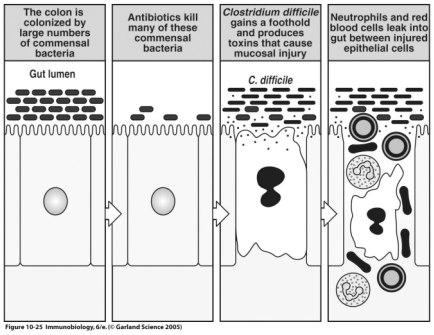


Figure 10-25 Immunobiology, 6/e. (© Garland Science 2005)

Some pathogens have evolved mechanisms that enable them to cross epithelial barriers

Salmonella typhi migrating through intestinal epithelium

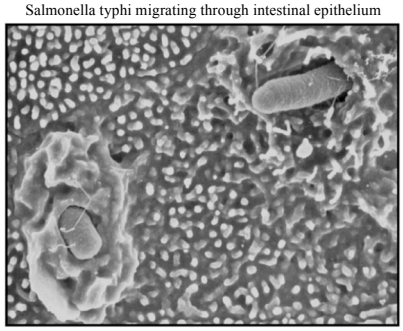
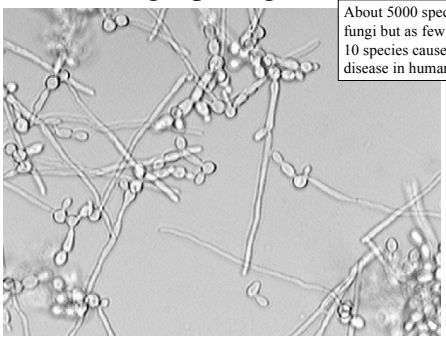


Figure 2-13 Immunobiology, 6/e. (© Garland Science 2005)

Fungal pathogens



About 5000 species of fungi but as few as 10 species cause disease in humans

Candida albicans fungi forming biofilm courtesy of Luis Murillo, UCSF

Fungi

Degree of infection can range from cutaneous to deep and systemic

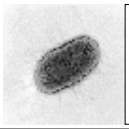
Many fungal infections are opportunistic
- i.e., the result of immunosuppression

Fungal infections are usually controlled by innate immunity

Components present in fungal cell walls activate innate immune system
- Lectin and alternative pathway of complement
- Phagocytosis - killing by reactive oxygen intermediates
- Recognition by TLRs leads to activation of phagocytes

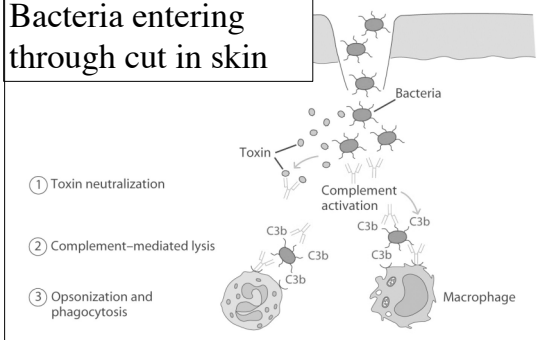
Bacteria

- Huge diversity of potentially pathogenic species
- Rapid replication
- Some species replicate extracellularly (e.g. E. coli)
- Other species replicate intracellularly (e.g. Listeria)



E. coli

Extracellular Bacteria entering through cut in skin



Phagocytic cells

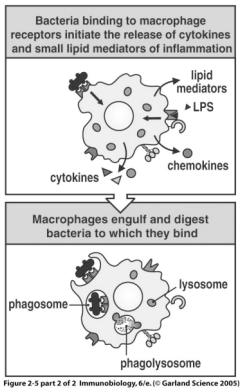


Figure 2-5 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Engulf pathogens either via pattern recognition, complement receptors, or Fc receptors.

Pathogens are killed by lysosomal proteases and reactive oxygen.

Complement

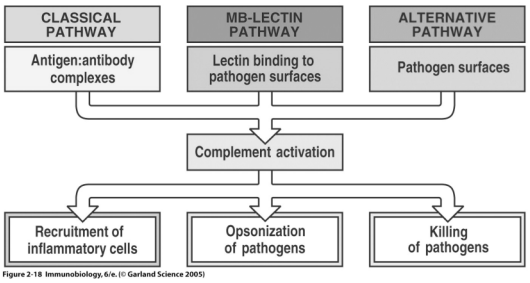


Figure 2-18 Immunobiology, 6/e. (© Garland Science 2005)

MBL is a pattern recognition molecule capable of initiating the complement cascade

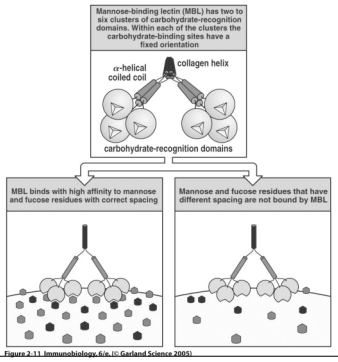


Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)

Recognition of conserved bacterial cell wall features by TLR2 and TLR4

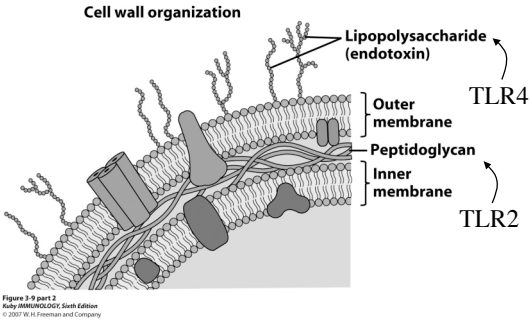


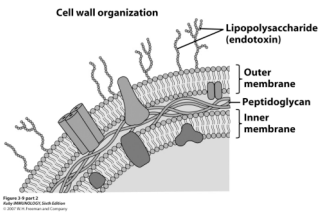
Figure 3-9 part 2
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company

Evasion of TLRs

Pathogens can modify targets of innate immunity

The gram-negative bacteria Salmonella and Yersinia can change their LPS structure, making it less stimulatory for TLR4.

Many pathogens down-regulate their flagellin genes upon entry into the host. This prevents recognition by TLR5.



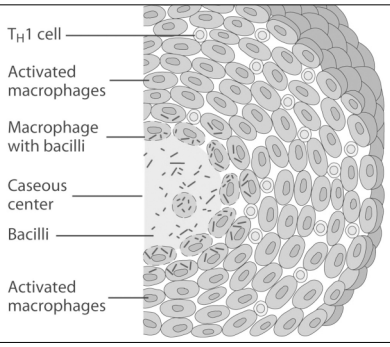
Extracellular Bacteria

- Innate immunity
  - Phagocytic cells, MBL and AP of C'
- Adaptive Antibodies Th2/B cells.
  - IgA→ block adherence to mucosa.
  - IgM and IgG→block adherence in tissues
  - IgM and IgG→neutralize toxins
  - IgM and IgG→act as opsonins
  - IgM and IgG→activate complement.

Pathogens in Endosomal Compartments
(bacteria and parasites)

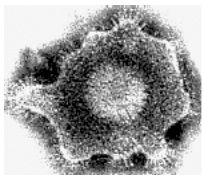
- ◆Innate immunity. Only before entering cell.
- ◆Adaptive Antibodies can block entry by neutralization, opsonize, activate C' etc.
- ◆Th1 produces CKs to activate macrophages.
- ◆CTLs are activated to kill infected target cells.
  - – Challenge to get endosomal antigens into Class I ag processing pathway.

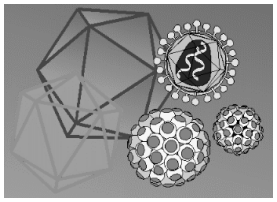
Pathogens in Endosomal Compartments
DTH role in Granuloma formation with Tb infection



Th1 and macrophage activation can resolve infection but can also result in tissue damage

Viruses





Icosahedral structure

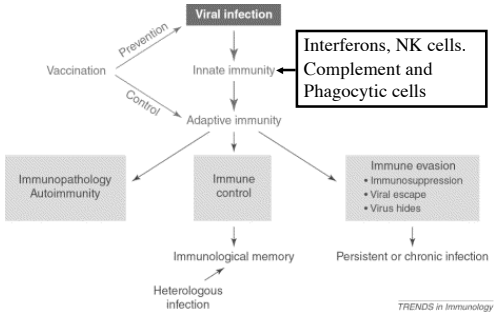
Protein structure (capsid) attached to nucleic acid (RNA or DNA).

Viruses

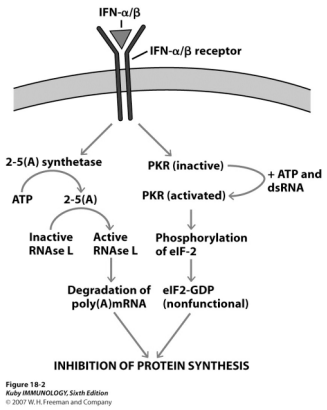
- ◆Viruses are obligate intracellular pathogens.
- ◆Variability among viruses.
  - – Enveloped and non-enveloped viruses.
  - – RNA vs DNA viruses.
  - – Some are simple with only 7 proteins some larger have 100s of proteins.
- ◆Viral nucleic acid is recognized as foreign by the innate immune system

  TLRs and cytosolic PRRs induce type I IFNs in response to viral infection

Viruses



Induction of type IFN-α/β by viral infection leads to host shutdown of protein synthesis



Immune Response to Viruses

Antibodies

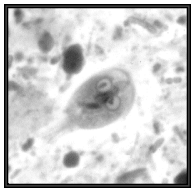
- **Neutralizing antibodies.** **IgG** block entry and prevent cell to cell spread of infection.
- IgA can block viral adherence and cell entry.
- IgM and IgG can activate complement lyse infected cells and enveloped viruses.

Cell mediated

- **CTLs.** CD8+ CTLs are most effective for elimination of virally infected cells.

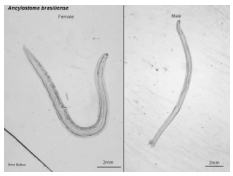
Parasites

Protozoa (unicellular)
Intracellular or extracellular



Giardia

Helminths (worms)
up to meters long



Ancylostoma (hookworm)

Immune Response to Protozoan Parasites

Innate immunity.

- Phagocytosis and C' activation.

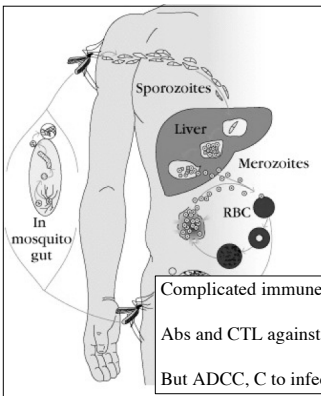
Adaptive

- Antibody elimination primarily through C' activation and opsonization.
- When extracellular- Th2 and B cell.

Intracellular Protozoan Parasites

- Leishmania live in macrophages and cell mediated immune response (DTH) is crucial for disease resolution (Th1 over Th2).
- Malaria is caused by different species of *Plasmodium* .

Malaria



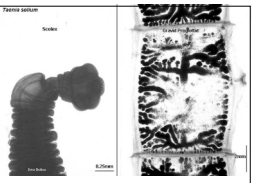
First cycle in liver then many rounds of replication in rbcs

Complicated immune response to Malaria.

Abs and CTL against liver infected cells.

But ADCC, C to infected rbcs

Large Helminths (worms)



Too large for phagocytosis BUT

Immune response can activate inflammation which results in expulsion of worms.

- Anti-worm IgE can activated degranulation of mast cells and eosinophils leads to Type I hypersensitivity like responses.
- Initiation of response is poorly understood. Unusual carbohydrates can be recognized by innate (complement) and adaptive (antibody) responses.

Helminths (worms)

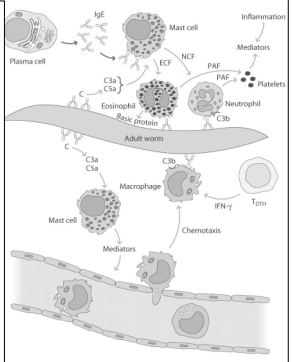
- Chronic exposure to antigens can cause chronic inflammation through.
  - Delayed type hypersensitivity (DTH) from Th1/activated macrophages can result in granulomas.

OR

  - Th2/B cell responses increase IgE, Mast cells, and Eosinophils which can activate inflammation.

Schistosomes (worms) Can have both Th1 (DTH) and Th2 for abs to worm infection.

Read in book about Schistosoma infections.



Immune Evasion

- Pathogens avoid the host immune response.
- Pathogens have co-evolved alongside an antagonistic immune response and have developed unique strategies to bypass and evade host immunity.

Evasion of Innate Immune Responses
Evading Complement

- Polysaccharide coat on bacterial cell wall often resistant to complement proteins.
- Vaccinia has protein which binds to C4b.
- Herpes simplex virus (HSV) has a glycoprotein which inhibits activity of C3b.
- Pseudomonas can inactivate C3a and C5a.

Evasion of Innate Immune Responses
Escaping phagocytic digestion

- Outer coat resistant to digestion.
  - e.g Mycobacteria tuberculosis.
- Inhibit fusion of phagosome with lysosome.
  - Mycobacterium, Legionella, Chlamydia.
- Resides in specialized vesicle.
  - Toxoplasma vesicle never fuses with lysosome.
- Escape from phagosome into cytoplasm.
  - e.g. Shigella, Listeria, Leishmania.

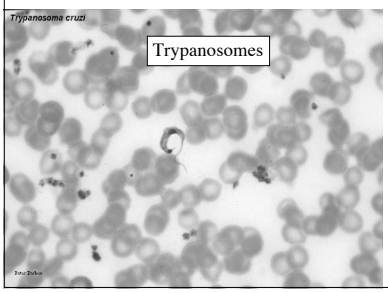
Evasion of antibody responses
Antigenic variation

Definition of antigenic variation

- Changes in the **antibody epitopes** displayed by the pathogen enable **escape** from antibody mediated responses.

Antigenic variation

Change in the antibody epitopes displayed by the pathogen allows escape from antibody mediated responses.

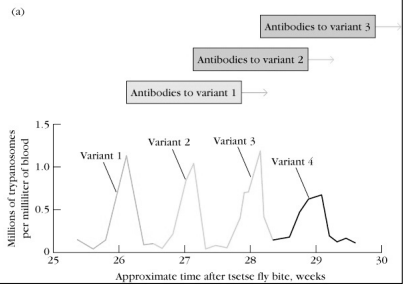


Beatty Rendition of Trypanosome

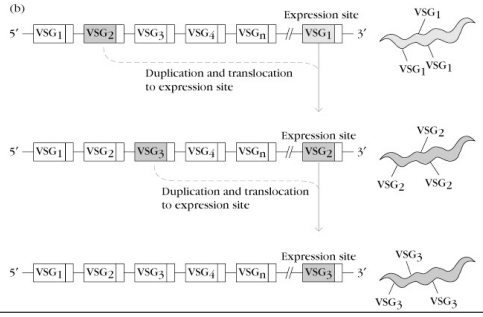
Antigenic variation
Variable surface glycoproteins (VSGs).

- Trypanosomes have multiple genes for same surface protein (>1000 VSGs).

When each VSG is expressed it covers surface of parasite and allows escape from antibodies.



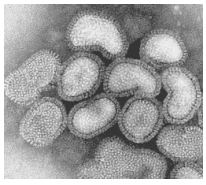
Different VSGs are inserted into a single expression site.



Antigenic variation- Other examples
Change in surface antigens

- Malaria evades immunity by sequential expression of variant proteins (var genes) on surface of rbcs.
  - Also Var gene products bind to VCAM-1, ICAM-1, E-selectin, which cause rbcs to bind to vascular endothelium to stop rbcs from circulating to spleen for degradation.

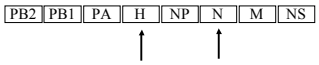
Antigenic variation
Influenza Virus



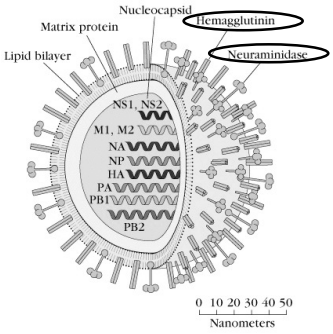
Orthomyxovirus

Single strand RNA Virus

Segmented genome



Influenza Virus Structure



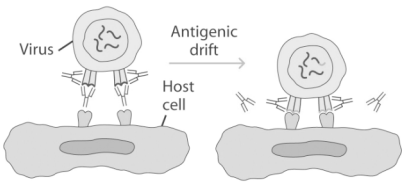
Influenza subtypes defined by surface antigens.
Hemagglutinin --H
Neuraminidase --N
e.g.
H1N1, H2N7, H3N1

Antigenic variation

Antigenic Drift

Neutralizing abs target Hemagglutinin(H)

Mutations in H allow escape from neutralizing antibodies.



H and N surface proteins have increased mutation rate.

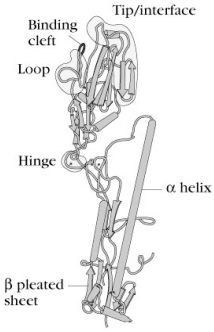
Antigenic variation

Antigenic Drift

- Point mutations in surface antigen epitopes decreases antibody binding.
- Antigenic drift occurs within a Influenza subtype.

Antigenic Variation

Antigenic Drift



Structure of Hemagglutinin (HA) Molecule of Influenza virus

Point mutations in key areas of HA to avoid antibody response.

Antigenic Variation

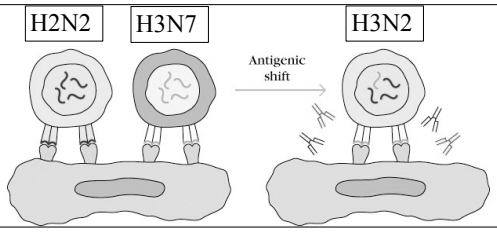
Antigenic Shift

- Influenza is a segmented RNA virus.
- Genetic reassortment can result in a new subtype of H and N.
  - The reassortment occurs when 2 viruses infect the same cell and new viral combinations can be made.
- A pandemic can result when a subtype never seen before in humans causes widespread disease and evolves human-to human transmission (e.g. H3N2 in 1968, avian flu soon?)

Antigenic Variation
Exchange of genetic material

Antigenic Shift

Two different viruses infect same cell allows genetic reassortment of subunits ---->new subtype.



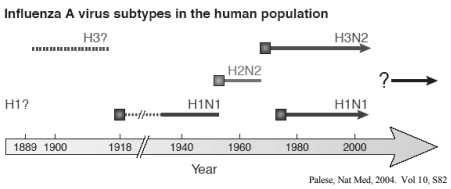
Influenza Virus Structure

TABLE 17-2 Some influenza A strains and their hemagglutinin (H) and neuraminidase (N) subtype

Species	Virus strain designation	Antigenic subtype
Human	A/Puerto Rico/8/34	H0N1
	A/Fort Monmouth/1/47	H1N1
	A/Singapore/1/57	H2N2
	A/Hong Kong/1/68	H3N2
	A/USSR/80/77	H1N1
	A/Brazil/11/78	H1N1
	A/Bangkok/1/79	H3N2
	A/Taiwan/1/86	H1N1
	A/Shanghai/16/89	H3N2
	A/Johannesburg/33/95	H3N2
	A/Wuhan/359/95	H3N2
	A/Texas/36/95	H1N1
	A/Hong Kong/156/97	H5N1

Influenza A viral strains causing epidemics identified based on their H and N expressing subtypes.

Influenza Virus Subtypes



Palese, Nat Med, 2004. Vol 10, S82

Is H5N1 next?
No good human-human transmission yet.

Antigenic Variation

Why we still have no cure or vaccine for the "common cold"!

- Distinct antigenic varieties (subtypes) all coated with different surface proteins.
- Need to make immune response to new virus subtype.
  - Example: rhinoviruses, coronaviruses cause common colds. These viruses are fast replicating viruses with a short incubation time.
  - SARS was caused by a coronavirus!!

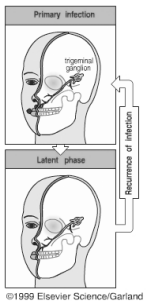
Evasion of Cell Mediated Immunity

Immune suppression

- By living in immune cells many pathogens can avoid host defenses as well as weaken immune responses.
- Examples:
  - HIV lives in T cells and macrophages.
  - EBV lives in B cells.
  - Leishmania live in macrophages.

Evasion of Cell Mediated Immunity

Latency

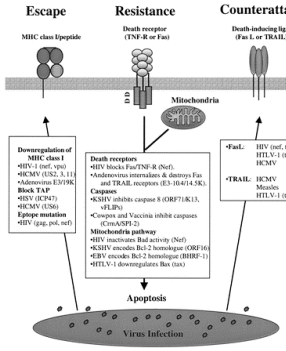


©1999 Elsevier Science/Garland P

HSV travels up nerve to ganglion where it remains latent until immune response wanes.

Immune suppression or stress reactivates virus it travels back down nerves where it can infect epithelial cells and spread.

Viral Evasion Molecules



Evading killing by CTLs and NK cells.

Escape
Class I MHC Modulation

- Down regulation of Class I MHC molecules.
  - HSV ----> ICP47 which binds to TAP.
  - CMV proteins, US11/US2, bind Class I MHC and target MHC molecules for proteolytic degradation.

Resistance
Viral-FLIP
(FLICE inhibitory protein)

- KSHV-FLIP inhibits caspase-8 activation which protects infected cells from Fas-mediated apoptosis.

Kaposi's Sarcoma Herpesvirus- KSHV

Counterattack
HIV Infected Cells - FasL

- HIV protein (**nef)** induces Fas Ligand expression on infected cells.
- Thus infected CD4 T cell kills Fas expressing HIV-specific CD8 T cell.