

## **Introduction to Viral Structure and Function**

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*The lecture was, for the most part, an oral rendition of the slides, so those who do not benefit from my format should just refer to the slides. Additionally, the slides include many pictures helpful in elucidation of viral structure and the nastiness of the diseases that they cause. The illustration of genital warts is not for the faint of heart. I heartily recommend a look. The first few slides contain a historical background which I have excluded here out of respect for our print quota as well as spite.*

### **Definitions**

virus – Latin for “slimy liquid” or “poison”

virus particle or virion – infection agent composed of nucleic acid (RNA or DNA), a protein shell (capsid), and optionally a lipid envelope

capsid – a protein coat of either icosahedral or helical symmetry that surrounds the viral nucleic acid and is composed of repeating subunits called *capsomeres*

nucleocapsid – the complete protein-nucleic acid complex (differentiated from an entire virion by the lack of the lipid envelope)

satellite or defective virus – requires a second (helper) virus for replication (e.g. hepatitis delta virus requires hepatitis B virus for replication, so the vaccination for hepatitis B is effective against both)

viroids – small, autonomously replication molecules of ssRNA circular in shape and consisting of 240-375 residues in length; plant pathogens

prions – *not viruses*; infectious protein molecules responsible for transmissible, sporadic, or familial spongiform encephalopathies (e.g. Creutzfeldt-Jakob disease, bovine spongiform encephalopathy = mad cow disease = vCJD in humans); pathogenic prion proteins (PrP<sup>Sc</sup>) can be formed from normal human proteins (PrP<sup>c</sup>) via post-translational processing

### **Viral Classification**

Older classifications were based on the location of pathogenicity: host, target organ, or vector of infection

Modern classifications (by International Committee on Taxonomy of Viruses) are based mostly on structure:

- RNA vs. DNA nucleic acid
- single strand (ss) or double strand (ds) nucleic acid
- replication strategy
- icosahedral or helical capsid symmetry (everything not icosahedral must be helical, it seems)
- presence or absence of a lipid envelope

### **Virion Morphology**

There is an illustration in the syllabus on page 4 which shows various virus morphologies, take a gander.

An overview of some viral families, their more famous members, their structure<sup>1</sup>, and some diseases they cause; for illustrations see slides:

- Paramyxoviridae (e.g. paramyxovirus) : (-) ssRNA, enveloped, helical
- Orthomyxoviridae (e.g. influenza virus) : (-) ssRNA segmented, enveloped, helical
- Coronaviridae (e.g. coronavirus → SARS) : (+) ssRNA, enveloped
- Filoviridae (e.g. Ebola virus) : (-) ssRNA, enveloped, helical
- Rotaviridae (e.g. rotavirus → infectious diarrhea) : dsRNA segmented, non-enveloped, icosahedral, double capsids
- Retroviridae (e.g. HIV) : 2 identical (+) RNA strands, enveloped, icosahedral capsid, helical nucleoprotein
- Hepadnaviridae (e.g. hepatitis B virus) : circular dsDNA with ss portions, enveloped, icosahedral
- Parvoviridae (e.g. B19 parvovirus → erythema infectiosum in children, rosy cheeks and fever): ssDNA, non-enveloped, icosahedral
- Papovaviridae (e.g. papillomavirus → cutaneous, cervical, and genital warts): circular dsDNA, non-enveloped, icosahedral
- Adenoviridae (e.g. adenovirus → conjunctivitis, tonsillitis) : linear dsDNA, non-enveloped, icosahedral
- Herpesviridae (e.g. Herpes Simplex Virus → keratitis, cytomegalovirus retinitis with hemorrhage around optic disk) : linear dsDNA, enveloped, icosahedral
- Poxviridae (e.g. poxvirus → smallpox, eradicated by world vaccination but now used as bioterrorism weapon) : linear dsDNA, enveloped, complex structure: part helical and part icosahedral

## Viral Pathogenesis

Elements of virus-host interaction

- similar to all other infections agents
- some viral strains more aggressive than others
- inoculum size may determine extent of disease
- route of exposure
- susceptibility of host in terms of pre-existent immunity from past exposure or vaccination (e.g. genital herpes is not as aggressive in hosts already inoculated with oral herpes) and host genetic factors
- immune status and age of host: neonates, elderly, and immunocompromised generally suffer more

Possible results of virus-host interaction

- a range of outcomes:
  - 1) no infection
  - 2) *abortive infection* with viral replication limited by host defenses, so no real disease
  - 3) asymptomatic infection
  - 4) symptomatic infection
  - 5) persistent, latent or self-limited infection depending on the agent and host immune competence
- influenced by availability of effective prophylaxis or therapy

Pathogenic steps in infection

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<sup>1</sup> It should be noted that the *capsid* is icosahedral or helical, but the *envelope* could be any weird shape outside of it

- overall: *inoculation* → *local replication* → *spread* → *viremia* ↔ *further replication* ↔ *further spread*
- virus may enter through skin, mucous membranes, respiratory tract, GI tract, transfusions, needle-stick, or maternal-fetal transmission
- local replication at site of inoculation, possible local pathology (e.g. herpes simplex virus cause ulcers at inoculation site)
- neurotropic agents may travel along nerve routes or reach CNS by viremic spread (e.g. speed of rabies virus reaching CNS depends on distance of site of animal bite to brain, faster at shoulder than at foot)
- for many agents, there is replication in regional lymph nodes with subsequent viremia and spread to target organs (e.g. herpes simplex virus travels from skin to dwell in dorsal root ganglia)
- target organs can be reached by traveling freely in plasma (e.g. picornaviruses) or associating with cells that go to the target organ (e.g. cytomegalovirus)
- replication in target organs may lead to local damage and further viremia
- non-specific and virus-specific host immune responses help downregulate viral replication

#### Immune responses to initial viral infection

- non-specific or innate immunity include phagocytic cells (neutrophils, monocytes, macrophages), cytokines (especially interferons), chemokines, natural killer cells, and other “antiviral” factors
- specific immunity include antibodies, *cytotoxic T-cells (most important)*, and antibody-dependent cellular cytotoxicity
- immunopathologic injury can occur even after viruses are all destroyed (e.g. after viral encephalitis)

#### Viral Persistence

- distinct from bacterial persistence
- viruses can cause chronic persistent infection in the face of an immune response (e.g. HIV, hepatitis B, hepatitis C viruses can reproduce and flourish despite the millions that are killed by immunity every day)
- immune compromise in the host may result in persistent infection where latency or elimination may have occurred in a healthy host
  - e.g. papillomaviruses, rubella virus
  - e.g. immunocompromising a patient with herpes virus will result in predictable ulcer flares even if the patient had never had sores when he was otherwise healthy<sup>2</sup>
- some virus cause latent infections characterized by a quiescent or minimally transcriptionally active viral genome (not producing the full syndrome) but with potential periods of reactivation
  - e.g. Herpesvirus, human retroviruses, and human papillomaviruses
- viruses exhibiting latency may also exhibit chronic, persistent infection in the setting of immune compromise
- mechanisms of persistent/chronic infections
  - antigenic variation to escape antibody or CTL responses (e.g. HIV)
  - downregulation of class I MHC
  - modulation of apoptosis
  - go to immuno-privileged sites
- latency can be achieved by decreased viral antigen expression and presentation to the immune system
- sites of persistence
  - nervous system (e.g. Herpes simplex virus and varicella-zoster virus in dorsal root ganglia, JC virus in brain, measles virus causing encephalitis)
  - liver (e.g. Hepatitis B, C, D viruses)
  - leukocytes (e.g. HIV, cytomegalovirus, Epstein-Barr virus)

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<sup>2</sup> UV light, such as that experienced by skiing or laying on the beach, stimulates herpes ulcer flares through an unknown mechanism, but does not cause the disease itself. For that, one may try the lodge hot-tub or the breezy seaside bungalow after sunset. Mmmmm..... BEWARE THE BUNGALOW!!

- epithelial tissue (e.g. papillomaviruses)

### **Oncogenic associations of viral infections**

- Epstein-Barr virus with lymphoma, nasopharyngeal carcinoma (China) and leiomyosarcomas in kids
- Herpesvirus 8 with Kaposi's sarcoma, body cavity B-cell lymphoma
- Hepatitis B and C viruses with hepatocellular carcinoma
- Human papillomavirus with cervical cancer and anogenital carcinoma
- HIV with Kaposi's sarcoma and lymphoma via immunosuppression

### **Diagnosis of viral infections**

- clinical suspicion is key
  - is syndrome diagnostic of a specific entity?
  - is viral disease in the differential diagnosis of a presenting syndrome?
- knowledge of appropriate specimens to send: blood, bodily fluids, lesion scraping, tissue (biopsy)
- viruses are fragile, so proper transport in specific media and swab, ASAP
- grow isolations in tissue cultures, animals, embryonated eggs to identify the virus
- rapid tests for acute setting
  - antigen detection in body fluids, blood, lesion scrapings, or tissue
  - nucleic acid detection in body fluids, blood, or tissue
  - antibody detection with presence of IgM or a 4-fold rise in IgG titer
- tissue biopsy for light microscopy supplemented by antigen and/or nucleic acid detection
- electron microscopy of body fluids or tissues (like a needle in haystack, so cannot rule out if negative)

### **Viral infection prevention and therapy**

- effective vaccines are one of the most significant advances in human health
  - smallpox nearly eradicated world-wide
  - polio, mumps, measles, rubella, influenza, hepatitis A, hepatitis B, varicella-zoster, rabies, adenovirus, Japanese B encephalitis, yellow fever, smallpox
- antibody (Ig) for prevention or amelioration of clinical disease in varicella-zoster, rabies, cytomegalovirus, respiratory syncytial virus, and hepatitis A (Ig in serum)
- blood screening for HIV, hepatitis B + C, CMV
- safe sexual practices can prevent many diseases (HIV, hepatitis B, human papillomavirus infections)
- specific antiviral therapy available for Herpes simplex virus, varicella-zoster virus, cytomegalovirus, HIV, influenza virus, respiratory syncytial virus, hepatitis B + C