Paramyxoviruses

- from Greek “myxa” = mucus
- “para” = other (as opposed to “ortho” -- next lecture).

Many human viruses in this family

**Paramyxoviridae**

- **Paramyxovirinae**
  - Respirovirus
  - Rubulavirus
  - Morbillivirus
  - Pneumovirus
  - Metapneumovirus

- **Pneumovirinae**
  - Parainfluenza, Types 1 and 3
  - Parainfluenza, Types 2 and 4
  - Respiratory syncytial virus
  - Human metapneumovirus

**Measles**

Morbilli = Italian for the "little disease" named in the middle ages. The "big disease" was the plague. Described since the 6th century.

Adapted from McIntosh and McAdam, NEJM, 2004

Be sure you know which strand is which

- Negative strand RNA viruses
  1. contain a polymerase within the virion
  2. have a mechanism to switch from mRNA synthesis to genome synthesis
  3. distinguish mRNAs from genomes

Non-segmented RNA, negative polarity (16 kb)

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1. attachment (H)
2. fusion (F) occurs at the plasma membrane
3. mRNA synthesis (L and P)
4. genome synthesis (L, P, and N)
5. assembly and budding (M)

Polymerase loads near the 3’ end of the RNA and transcribes until it comes to a polyU stretch. There is no primer. It then “stutters” and adds a polyA tail, skips the intergenic region, and starts to transcribe the next gene.

Polymerase sometimes fall off the template before it can re-initiate at the next gene. This creates a gradient of mRNA concentrations which leads to a gradient of protein concentrations.

N>P>M>F>H>L (note more structural proteins than enzymatic proteins)

Three (or more) proteins from the P gene

Polymerase adds a non-templated “G” such that the C-terminus of V is in a different reading frame from P.
When the levels of N protein are high enough, it coats the newly made RNA and causes the polymerase to skip the start and polyA signals in the intergenic regions. Now, full-length + strand RNA is made.

which is then used as a template for new genomic (-strand) RNA

Measles virus cellular receptors

- **CD46**
  - Interacts with H protein of vaccine isolates of MV but not primary isolates.
  - Widely expressed.

- **SLAM (CD150)**
  - Interacts with H protein of vaccine and pathogenic primary isolates of MV
  - Signaling Lymphocytes Activation Molecule : glycoprotein expressed by activated T and B lymphocytes and dendritic cells

- **Nectin-4**
  - Receptor on polarized epithelial cells responsible for transmission by aerosol droplets

Measles virus spread into and out of the body

MV enters the airway, infects macrophages and dendritic cells which ferry the virus to the local lymph nodes

Virus spreads to lymphatic organs, thymus and spleen

Infection spreads to the epithelium in the airway

Progeny viral particles are released in the trachea and expelled by coughing and sneezing

doi:10.1038/nature10639
Measles pathogenesis

- Measles causes a profound transient immunosuppression
- The cause of death is usually of subsequent complications from other infections and dehydration
- 1 in 1,000 cases results in a post-infection encephalitis (autoimmune in nature--perivascular demyelination). Often fatal.
- 1 in 300,000 cases results in a persistent infection of the central nervous system called subacute sclerosing panencephalitis (SSPE). Occurs 7-10 years after initial infection.

Measles Pathogenesis

- Severe, but transient immunosuppression
- Infection and severe depletion of T cells in the gut
- Immunosuppression thought to be a direct result of lymphoid cell killing by the virus
- Death by opportunistic infections

The measles paradox: increased deaths from other infectious diseases years after measles

Due to reduction in memory T cells during acute measles infection
HIV and Measles Pathogenesis

- Severe immunosuppression
- Infection and severe depletion of T cells in the gut
- Death by opportunistic infections

Measles is only acute--almost no chronic infection (persistence)
- Immunosuppression improves eventually (weeks to months)
- Cell types infected overlap, but are not identical

Measles is the most contagious human viruses known

- $R_0$ for measles virus is 15! Transmission by airborne droplets.
- A population size of ~500,000 is necessary to maintain the virus (= 16,000 newborns/year)
- If the population is smaller, then the epidemic would burn itself out when all susceptibles have been infected

Effect of population size on measles epidemics

![Graph showing the relationship between population size and the percent of months with cases of measles.](image)

Each dot represents a different island population (data from 1949-1964). Measles epidemics are not sustained when the number of new susceptibles (newborns) is less than 16,000/yr.

Guam and Bermuda are exceptions because of the influx of outside visitors.

Measles virus could not have existed as an endemic infection of humans until ~5000 years ago

- human population density became sufficient to support it
- population centers in the Fertile Crescent?
- domestication of cattle?

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Viruses and Human Disease, Straus and Straus

Estimated 56 million deaths in S. America in the 17th century.

Viral emergence relates to anthropogenic factors in the Americas and Africa.
Measles is controlled by vaccination in most places, but common in India and central Africa

- Severe measles is particularly likely in poorly nourished young children
- Mortality is 0.1% in the US (although 20% require hospitalization) but up to 10% in the developing world.
- There is a safe vaccine that is efficacious (98%) and costs only 30¢ per dose
- The primary reason for continuing high childhood measles mortality is the failure to deliver at least one dose of measles vaccine to all infants.
  - (itis actually a little more complicated than that, see later)


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Measles vaccine, John Enders

David Edmonston, 11 yo boy with measles

13 passages in human kidney and monkey cells

“wt” Edmonston strain

24 passages in human kidney cells

28 passages in human amniotic cells

Humans are the only known host, so..

6 passages in chicken eggs (no plaques seen for first 5 passage)

13 passages in chicken embryo fibroblasts

Edmonston-seed A and B (still causes fever)

>40 passages in CEF at 32°C

~30 mutations relative to “wt” Edmonston.

Attenuation is not simple. A combination of receptor use (H protein) and interactions with IFN induction (C protein), M protein mutations affecting interactions with nucleocapsid, some L protein changes important.

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Measles Cases, United States, 1950-2004

new policy to give second dose of vaccine before starting school

Measles vaccine is now given at 9 months and ~5 years as part of a trivalent MMR (measles, mumps, rubella) vaccination

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Annual reported measles cases and MCV1* and MCV2** coverage, 1980-2015

Dramatic drops in Measles cases, but recent stagnation

Source: WHO/IVB database, 2015

194 WHO Member States.

Updated on 15 July 2015
Measles outbreaks in populations with partial vaccine coverage

May 2005, a 17 yr old unvaccinated girl from Indiana returned from a trip to Romania and attended a church gathering with 500 people.

Of ~50 unvaccinated people at the gathering, 36 became infected.

To eliminate measles it is necessary to achieve complete worldwide coverage.

Problems to overcome for world-wide immunization against measles:

- Infants are protected by maternal antibodies for the first 6-12 months of life. So, vaccine cannot be given at birth (i.e. give too early and vaccine does not work).
- However, if it is given too late, then all infants will get infected with wild measles in communities where the virus is endemic.
- Coverage needs to be nearly complete.
- Periods of partial coverage are particularly dangerous because of reduced maternal protection (infants are more at risk than older children).

Things you should know about Paramyxoviruses:

- Basic replication steps
  - Negative strand virus requirements
  - mRNA production
  - Switch to genome production
  - How are genes regulated?
- Why you need a large population size to sustain measles.
- Pathogenesis.
- Vaccine and virus elimination issues.
- Discussion paper
  - (TCID$_{50}$ = Tissue culture infectious dose 50 = amount of virus necessary to infect 50% of wells. Used as a dilution assay to determine the amount of infectious material in a sample and to standardize infections).
  - What were the questions they set out to answer using their 3 color viruses?
  - What did they find?
  - What were other possible outcomes for the transmission experiments and what does this result show?
  - What can they do next with this system?