Filoviridae & the Ebola Virus
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Lecture Overview
- Structure
- Virus Replication Cycle
  - Protein Synthesis
- Pathogenesis

Filoviridae Family
- *Filo:* from Latin meaning threadlike
- Structurally & Genetically similar to Rhabdoviridae and Paramyxoviridae
- Two Genera:
  - Marburg-like virus
  - Ebola-like virus

Structure
- Pleomorphic, Filamentous
- Striated
- 80nm diameter
- 130-140,000nm long
- Enveloped

Genome
- Negative Sense ssRNA
- Unsegmented
- 7 proteins
- Gene overlap

Ebola Virus Proteins
- GP- Transmembrane glycoprotein
- NP- Nucleoprotein necessary for capsid assembly
- VP24- Anti-viral inhibitor?
- VP35- Inhibits IFN production
- VP30- Transcription anti-terminator
- VP40- necessary for capsid assembly and budding
- L- Viral Polymerase
Replication Cycle

1 Host Entry
- Contact with infected bodily fluids
- Enters through mucous membrane or directly into blood (needle stick)
- No confirmed spreading of virus by aerosol in nature

Replication Cont.

2 Adsorption- Glycoprotein (GP₁) binds cellular receptor
- Mediated by cellular cofactors, i.e. folate receptor α
- Mononuclear phagocytic cells & monocytes are primary targets

3 Endocytosis
- pH lowering in endosome
- GP₁ mediates membrane fusion; release of viral particle into cytoplasm

Replication Cont.

4 Protein Synthesis
- Requires viral polymerase (L)
- VP30 anti-terminator allows transcription of genes downstream from first gene (Ebola Only)
- VP35 prevents anti-viral response to dsRNA

-GP synthesis
- Complex post-translational processing
  - O-linked/N-linked glycosylation
  - Proteolitic cleaving by proteases
  - Aylation

Ebola Glycoprotein

- GP₁/GP₂- transmembrane protein
  - Binding/Fusion
- sGP- truncated soluble protein (Ebola Only)
  - Secreted
  - Decoy for immune system?
- Give rise to neutralizing & protective antibody

Replication cont.

5 Virus Assembly & release - Exact mechanism not known
- NP essential for RNA packaging
- VP40 essential for Budding at membrane
- VP40 and GP give filamentous morphology

Complete Virion contains:
- ssRNA, NP, VP35, VP24, L, VP30 (Ebola Only)
Ebola Virus: Interactions With Immune System

- Innate Immune System
- Monocytes Primary targets
  - Carry virus throughout body
  - Lysis releases cytokines
- Early infection of Dendritic Cells
  - Delays specific immune response

Interaction with Immune System Cont.

- Over expression of proinflammatory signals
  - Cytokines
  - Does not clear infection
- VP35 inhibition of IRF3
  - No transcription of IFN genes
  - No antiviral response to dsRNA
- Inhibition/Destruction of immune cells
  - Neutrophils & macrophages

Pathogenesis

- Glycoprotein responsible for CPE of virus
  - Breakdown of extracellular matrix
    - Rounding and detachment of endothelial cells
    - sGP inhibits Neutrophils
  - Evidence suggests virus does NOT directly cause most of the disease pathology

Pathogenesis

- Massive Immune Response
- Activation of macrophages and monocytes
  - Clumping may cause coagulation observed in some clinical cases
  - Proinflammatory signals released
    - Cytokines, TNF, IFN
    - Breaks downs endothelial barrier
    - Blood leaks into tissue- blood pressure drops-Shock most frequent cause of death.

Ebola Hemorrhagic Fever

- 2-21 day incubation period
- Abrupt onset: flu-like symptoms
  - Fever, headache, muscle aches, stomach pains
- Rash, red eyes, internal/external bleeding
- Death (50-90% according to WHO)

Ebola Hemorrhagic Fever

- Not known why some are able to survive
- Larger Early Immune response in those that do
- Virus May remain up to 3 months
  - Convalescents potential human reservoir
  - Virus present in seminal fluid
Treatment/Vaccine

- No effective treatment
  - Research on treating inflammatory immune response
    - Anti-INF, Anti-cytokine antibodies
    - Steroids
- No approved vaccine
  - GP protective antibodies
    - Also immunosuppressive

Ebola as a Biological Weapon

- As late as 1992 Russia was producing large quantities of Ebola virus for use as a weapon.
  - No vaccine
  - No treatment
  - High infectivity (as few as 17 particles necessary to cause disease)
    - Can potentially be spread by aerosols
- Japanese Terrorist Cult, Aum Shinrikyo, unsuccessfully attempted to obtain Ebola virus

References

1 Filoviruses. University of Leicester Department of Microbiology. www.micro.msb.le.ac.uk/3035/Filoviruses.html