

# Filoviridae & the Ebola Virus

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## Lecture Overview

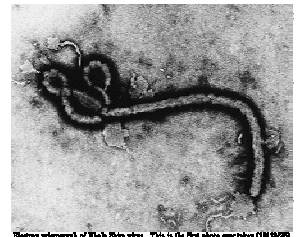
- Structure
- Virus Replication Cycle
  - Protein Synthesis
- Pathogenesis

## Filoviridae Family

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

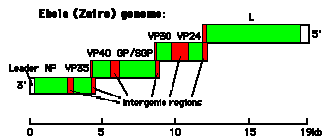
## Structure

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



Electron micrograph of Ebola Virus. This is the first photo ever taken (1976) by Dr. T.A. Marburg, now at CDC, during the 1976 outbreak in the Congo.

## 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<sup>2</sup>
  - 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 (GP<sub>1</sub>) binds cellular receptor<sup>3</sup>
  - Mediated by cellular cofactors. i.e. folate receptor  $\alpha$
  - Mononuclear phagocytic cells & monocytes are primary targets<sup>4</sup>
- 3 Endocytosis
  - pH lowering in endosome
  - GP<sub>2</sub> mediates membrane fusion; release of viral particle into cytoplasm

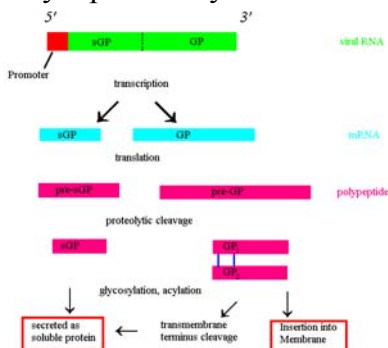
## Replication Cont.

- 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<sup>5</sup>
- GP synthesis<sup>1</sup>
- Complex post-translational processing
  - O-linked/N-linked glycosylation
  - proteolytic cleaving by proteases
  - acylation

## 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

## Glycoprotein Synthesis



## 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<sup>6</sup>
  - 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 down 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

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- 2 Center for Disease Control *Ebola Hemorrhagic Fever*. [www.cdc.gov/ncidod/dhvd/publications/ebola.htm](http://www.cdc.gov/ncidod/dhvd/publications/ebola.htm)
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