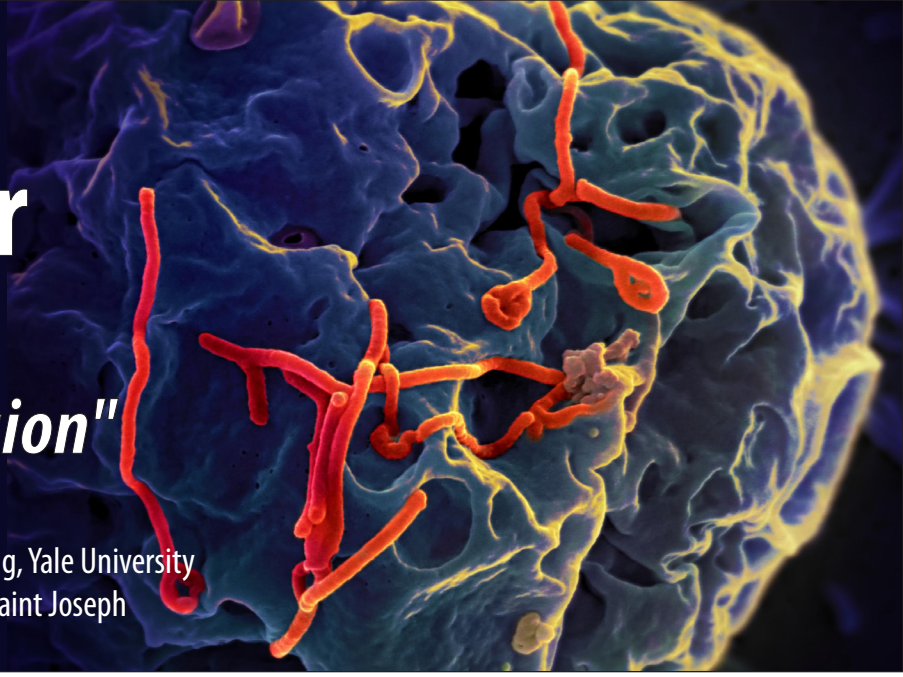
NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Preparing for

"The Ebola Wars: Mission Immune Evasion"



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The following information is intended to prepare you for the case study "The Ebola Wars: Mission Immune Evasion." After reading this document, you should be able to:

- List the major Ebola genes involved in the evasion of the host cell immune response.
- Explain the role of the proteins encoded by Ebola genes in evading the immune response.
- Describe the relationship between gene placement and expression level.
- Explain the necessity of the host cell in viral replication.
- Describe defenses that the host cell deploys against Ebola virus infection.

The Ebola virus is a pathogen that causes human disease with a high mortality rate. The Ebola virus genome is a negative sense single-stranded RNA containing seven genes (see Figure 1). During replication within a cell, gene expression follows a gradient with the genes nearest the 3′ end of the genome having increased transcription compared to those nearer the 5′ end. The virus particle itself takes a filamentous form, ranging up to 1 µm in length (see Figure 2). The exterior of the virion is a host cell-derived lipid envelope studded with trimeric GP. Directly beneath the lipid envelope are the structural proteins VP40 and VP24, which help define the filamentous shape of the virus. Internally, non-structural proteins L and VP35 are associated with the RNA genome bound by NP and VP30.

Like all viruses, Ebola viruses cannot replicate without infecting a host. Ebola virus is transmitted between humans through bodily fluids, including but not limited to blood, saliva, and semen.

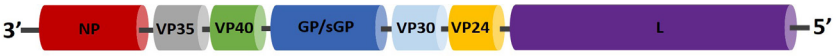

Figure 1. Negative strand RNA genome of the Ebola virus.

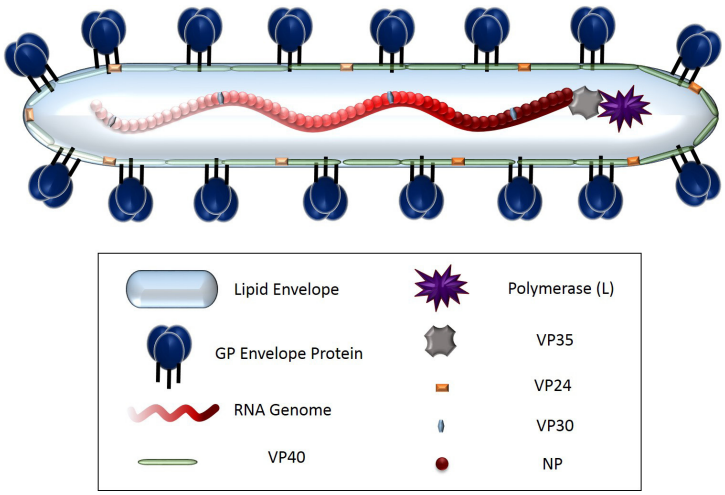

Figure 2. The Ebola virus particle.

Once a virus has entered a new potential host, macrophages and dendritic cells are commonly the first cells infected. These cells become "viral factories," replicating the virus and releasing particles into the extracellular environment of the host. Subsequently, nearly all cell types and tissues within the human host can be infected by the virus, with the notable exception of B and T lymphocytes (though these can be affected indirectly). Both the innate immune system (including macrophages, dendritic cells, NK cells, and the production of cytokines (notably interferon-γ)) and the adaptive immune response (including cytotoxic T cells and antibody-producing B cells) are activated in the human host, and the efficacy of these responses appears to be directly associated with the outcome of disease. Indeed, in many ways it is a battle between the host immune response and the Ebola virus which attempts to overcome that response.

Three Ebola virus genes, *GP, VP35*, and *VP24*, are directly implicated in evading the immune response of host cells. Due to post-translational processing, the *GP* gene can yield two proteins, GP or secreted GP (sGP). GP inhibits the cellular protein tetherin, which attempts to keep new viruses from being released from the cell. sGP is released from infected cells and can soak up anti-GP antibodies produced by host cells as a counterattack. Additionally, when a host is infected it can release interferons, chemicals that alert other immune cells to accelerate the response. Ebola virus proteins play a role in silencing interferon signaling (VP24) and blocking the production of interferon (VP35), effectively making it appear that infection by the Ebola virus has not occurred. Moreover, VP35 has roles in protecting the temporary viral double-stranded RNA that is produced during genome replication, and in preventing RNAi degradation of Ebola virus mRNAs. In the end, the war between these Ebola virus weapons and the immune response plays a large role in determining if the infected host survives.

Useful Resources

Centers for Disease Control and Prevention. 2017. Ebola (Ebola Virus Disease). http://www.cdc.gov/vhf/ebola/index.html.

Misasi, J. and N.J. Sullivan. 2014. Camouflage and misdirection: the full-on assault of Ebola virus disease. *Cell* 159: 477–86. http://www.cell.com/cell/fulltext/S0092-8674(14)01293-8.

Sanchez, A., M.P. Kiley, B.P. Holloway, and D.D. Auperin. 1993. Sequence analysis of the Ebola virus genome: organization, genetic elements, and comparison with the genome of Marburg virus. *Virus Res.* 29, 215–40. https://doi.org/10.1016/0168-1702(93)90063-S.