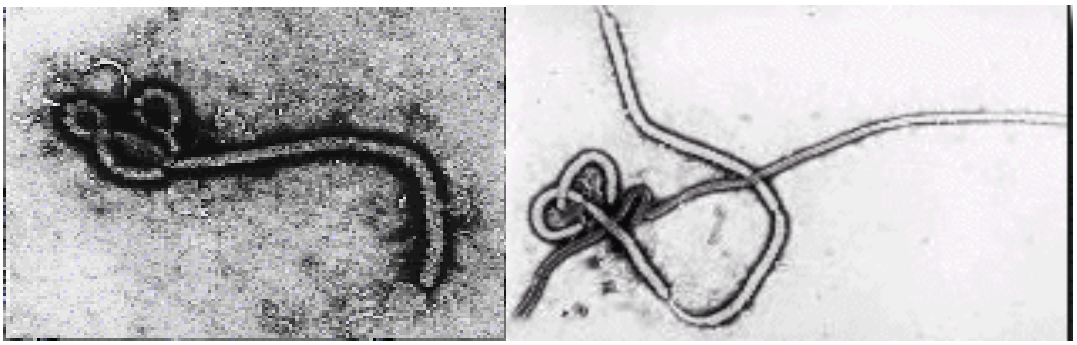
EBOLA

Overview of the Virus Ebola

Ebola belongs to a family of viruses entitled Filoviridae, and is commonly classified as a viral hemorrhagic fever (CDC, 2002). The known causes of viral hemorrhagic fever include arenaviruses, filoviruses, bunyaviruses, and flaviviruses. All virions classified as hemorrhagic are enveloped (covered) RNA viruses, whose survival is dependent on an animal reservoir. Viral hemorrhagic fever commonly describes a medical scenario in which multiple organ systems of the body are affected as well as extensive internal hemorrhaging (bleeding) (WHO,2000).

Ebola along with the Marburg virus are the only viruses identified in the Filoviridae family (CDC,2002). Filovirus virions are characterized by having one molecule of single stranded, negative-sense RNA, as well as their unique "U" shaped structures (CDC, 2002).



Figures 1 and 2 *show scanning electron micrographs of Ebola. Figure 1 was the first photograph ever taken of Ebola in 1976.*

There are four known constituents of Ebola namely: Ebola-Zaire, Ebola-Sudan, and Ebola-Ivory Coast. The fourth, Ebola-Reston (CDC,2002). Only three of the four forms listed above are known to cause disease in humans. Ebola Reston is characterized as a

non-human primate infections disease. Ebola itself has an average length 920 nm and a diameter of 80 nm (WHO,2000). The virus is considered a level 4 biohazard and is only handled in the most sterile environments in full protective suiting. Ebola is spread through direct contact with blood or other bodily secretion of infected people (CDC, 2002) (WHO, 2000). This close proximity infection, makes outbreaks among small communities and families very common. Infection can also be caused through contact with contaminated medical equipment such as needles, glassware, no sterile equipment, or careless lab procedures.

Acute infection of humans with Ebola , one principal etiologic agents of hemorrhagic fevers, often results in a paradoxical pattern of immune responses: early infection, characterized by an outpouring of inflammatory mediators such as TNF-α, TL-10, and IL-6, vs. late stage infections, which are associated with poor immune responses. The mechanisms underlying these diverse outcomes are poorly understood. In particular, the role played by cells of the innate immune system, such as dendritic cells (DC), is not known,. In this study, we show that Ebola viruses infect human monocyte-derived DC and impair their function. Monocyte-derived DC exposed to either virus fail to secrete proinflammatory cytokines, do not up-regulate costimulatory molecules, and are poor stimulators of T cells. These data represent the first evidence for a mechanism by which Ebola virus target DC to impair adaptive immunity.

Data from in vitro experiments and animal models suggest that Ebola infect macrophages and endothelial cells early in infection . Infection of these cell types, two principal players of the innate immune system, are believed to act as critical triggers for

the rapid and uncontrolled secretion of inflammatory mediators (2, 3, 8, 9), However, despite the systemic release of Inflammatory
mediators that occurs following infection with Ebola, severe or fatal diseases are often associated with a generalized suppression of adaptive immunity, as evidenced by the low specific Ab and poor cellular immunity.

Symptoms characterizing Ebola are unspecific in the first few days of the infection, making the virus even more dangerous. Infection is marked by initial signs of fever, fatigue, exhaustion, muscle aches, and dizziness (WHO,2000). As the disease progress bleeding under the skin, in internal organs, and from the eyes, ears, and mouth are seen. Patients with severe progressions of the disease express symptoms of shock, delirium, coma, seizures, and nervous system malfunction (CDC, 2002). The Ebola virus is diagnosed by specific antigens detected in blood specimens, isolation of virus in cell cultures, or detection of IgM and IgG antibodies(WHO,2000) . ELISA tests are often used to diagnose the viruses. It should be noted that all tests are conducted in the most stringent laboratory conditions in order to protect scientists and other patients. There is no established treatment for Ebola. Infected patients are treated using antiviral drugs (ribavirin) as well as generally supportive therapy that replenishes intravenous fluids, maintains blood pressure, and other bodily functions (CDC, 2002). Below is a 3D image of Ribavirin, a drug commonly used in treatment of hemorrhagic fevers, that acts as an RNA mutagen on the virion particles.

Ebola and the Immune System

Interaction of Ebola with the immune system is essential to understanding the pathogenesis of the virus. One of the characteristics of infection with the Ebola virus is the destruction of the immune system. The majority of patients infected with the virus are unable to develop sufficient immune responses. This is mainly attributed to the viruses infection of the fibroblastic reticular system, which plays a role in maximizing immune responses (Takada, 2001). Scientists speculate that disruption of cytokine production is affected by infection of both fibroblastic reticular system and mononuclear phagocytes, in addition to disruption of antigen trafficking (Takada, 2001). It is also thought that transmission of virions between tissues is partially due to infection from macrophages and circulating monocytes.

One of the primary failures of the immune system in regards the Ebola virus, is the inability to activate T-cells early in the course of the infection resulting in an insufficient humoral response which include both antibody and cytokine responses(Takada, 2001). Another result of the failure to activated T-cells adaquately is apoptosis of blood leukocytes (Takada, 2001). These characteristics of Ebola infection are commonly associated with fatality in patients. In both fatally infected patients and experimentally infected monkeys, the virus was found to cause extensive damage to lymph nodes, spleen, and bone marrow. Patients surviving infection by Ebola virions were found to develop stronger antibody responses in the early stages of infection than patients who eventually succumbed to the disease (Takada, 2001). The role of the innate immune

response in the first few days of infection is considered very important in control of viral replication. Conversely up regulation of interluken 2, 10, tumor necrosis factor, and interferons are associated with infection of the Ebola virus (Takada, 2001) . Although their role is poorly understood, antibodies are thought to play an essential role in inhibiting infection of Ebola (Maruyama, 1999). Antibodies have been found that bind to the nucleoprotein, the envelope protein, and the secreted envelope glycoprotein (see Fig. 4 below). Studies have shown that neutralizing antibodies made in response to these glycoproteins are effective against the Ebola virus and show some promise in designing a vaccine (Maruyama, 1999).

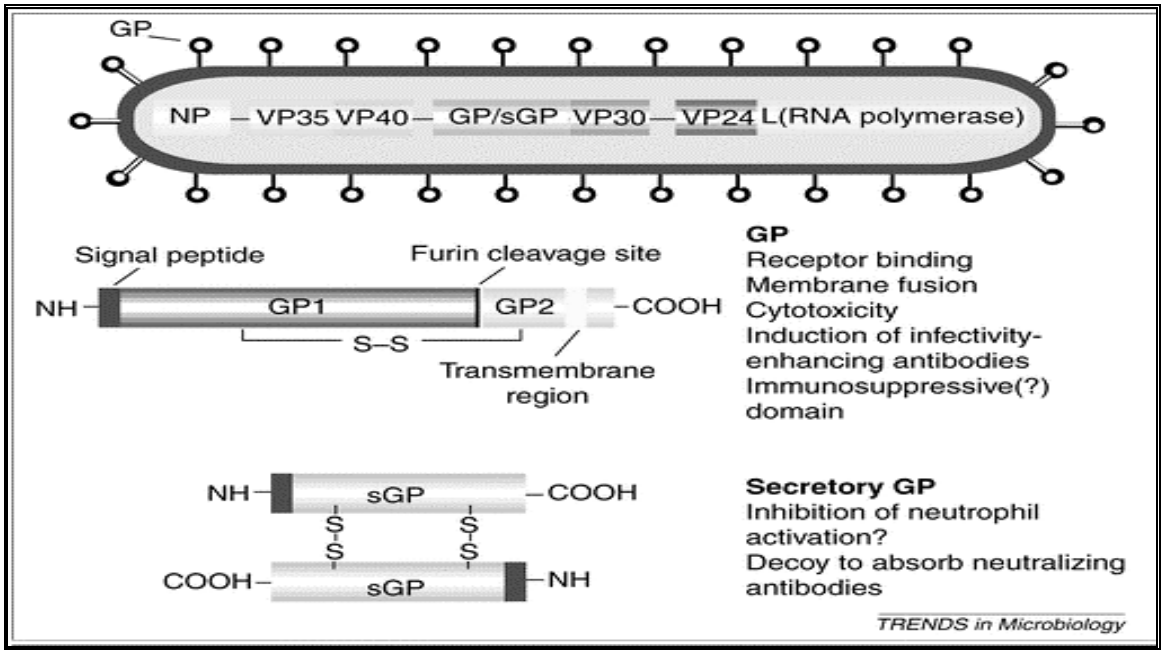


Figure 56 *shows a protein map of Ebola virus RNA. (Takata, 2001) permission pending.*

VP35 (see diagram above) is thought to play a pivotal role in the synthesis of viral RNA, serving as an interferon antagonist. The production of INF antagonist is thought to be an essential factor to increasing the pathogenicity of the Ebola Virus. There is a very strong possibility that the potency of VP35 could account for the varying degrees of virulence among different strains of the Ebola virus(Takada, 2001). Immunsupression of the Ebola

virus is largely attributed to a section of the glycoprotein (see diagram above: G1 and G2), which shares a strking homology to another immunosuppressive protein found in oncogenic retroviruses(Takada, 2001). This particular sequence is thought to aid the Ebola virus in evading the human immune responses in addition to suppressing the major histocompatibility complex (MHC) (Takada, 2001).

Protection against Lethal Ebola Virus Infection

Ebola virus is a highly lethal human pathogen and is rapidly driving many wild primate populations toward extinction. Several lines of evidence suggest that innate, nonspecific host factors are potentially critical for survival after Ebola virus infection.
Here, we show that nonreplicating Ebola virus-like particles (VLPs). containing the glycoprotein (GP) and matrix protein virus protein (VP)40, administered 1-3 d before Ebola virus infection rapidly induced protective immunity. VLP injection enhanced the numbers of natural killer (NK) cells in lymphoid tissues. In contrast to live Ebola virus.
VLP treatment of NK cells enhanced cytokine secretion and cytolytic activity against NK-sensitive targets. Unlike wild-type mice, treatment of NK-deficient or depleted mice with VLPs had no protective effect against Ebola virus infection and NK cells treated with VLPs protected

against Ebola virus infection when adoptively transferred to naive mice. The mechanism of NK cell-mediated protection clearly depended on perform, but not interferon-* secretion. Particles containing only VP40 were sufficient to induce NKcell responses and provide protection from infection in the absence of the viral GP. These findings revealed a decisive role for NK cells during lethal Ebola virus infection. This work should open new doors for better understanding of Ebola virus pathogenesis and direct the development of immunotherapeutics. which target the innate immune system, for treatment of Ebola virus infection

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