

CLINICAL IMPLICATIONS OF BASIC RESEARCH

How Ebola Virus Infects Cells

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Despite its isolation three decades ago, Ebola virus continues to cause periodic outbreaks of severe hemorrhagic fever in humans, and the closely related Marburg virus is responsible for a recent outbreak of disease in Angola. The mortality rate associated with Ebola virus infection can reach 90 percent, and so the prospect of an effective therapy is attractive. A recent study by Chandran et al.¹ sheds light on the molecular events that culminate in infection and may thus lead to a new approach to therapy.

Embedded within the host-derived lipid envelope of Ebola virus are glycoprotein spikes that bind to cells and mediate fusion between the viral envelope and the host cell membrane, enabling the virus to release its contents into the host-cell cytoplasm. Although some viruses, such as paramyxovirus and human immunodeficiency virus (HIV), fuse with the plasma membrane, others — including Ebola virus and influenza viruses — are taken up into the endosome, where they are exposed to a low-pH environment and cross the endosomal membrane to reach the cytoplasm.

Conformational changes must take place in the viral glycoprotein spikes to allow its hydrophobic fusion domain to be inserted into the host cell membrane. These conformational changes serve as a switch that initiates the fusion of the virus to the host cell.

Before Chandran et al.¹ released their findings, only two mechanisms were known to trigger conformational changes in viral fusion proteins. The induction of changes by means of a low pH is exemplified by the hemagglutinin of influenza virus.² After binding to the cell surface, influenza virus is internalized by endocytosis. The acidic environment in the endosome induces conformational changes in the viral hemagglutinin, allowing it to mediate fusion between the viral envelope and the endosomal membrane. A different mechanism is illustrated by the envelope glycoprotein 160 (GP160) of HIV, which consists of two domains: a domain that binds the GP120 receptor and a GP41 fusion do-

main. After GP120 binds to its receptor molecule CD4, it binds to coreceptors such as the chemokine CCR5, triggering a conformational change in the entire protein and enabling GP41 to initiate fusion between the viral envelope and the cell membrane.³

Chandran et al.¹ propose a third triggering mechanism (Fig. 1). They discovered that proteolysis by two endosomal cysteine proteases, cathepsin B and cathepsin L (which are active in a low-pH range), renders a conformational change in the surface glycoprotein of Ebola virus. They showed that glycoprotein-mediated infection is substantially reduced in cells lacking these proteases; that cathepsin B and cathepsin L can individually cleave Ebola virus GP1 to yield an approximately 18-kD N-terminal fragment, which is further digested by cathepsin B; that the extent of viral infectivity mediated by glycoprotein is correlated with the efficiency of the production of the 18-kD fragment; and that selective inhibitors of cathepsin B and of both cathepsin B and cathepsin L block viral infection in cultured cells (Fig. 1). Their model therefore predicts that after the internalization of Ebola virus into the endosomes of cells, the C terminus of the viral GP1 is removed by cathepsin B, cathepsin L, or both in the endosome, leaving the 18-kD N-terminal fragment. Subsequent digestion of this fragment by cathepsin B initiates membrane fusion by GP2, the still-intact fusion domain of the glycoprotein molecule.

An experimental vaccine for this disease is now being evaluated,⁴ and treatment of experimentally infected nonhuman primates with a recombinant inhibitor of factor VIIa or tissue factor yields a 33 percent survival rate under conditions that are lethal to nearly all nontreated animals.⁵ Despite these encouraging results, there still are no antiviral drugs (not even experimental ones) available for clinical use. The findings of Chandran et al.¹ are therefore notable not only from a basic-science perspective, but also from other perspectives, because they point to a new direction in the treatment of this infection. Although the cathepsin inhibitors used in this study

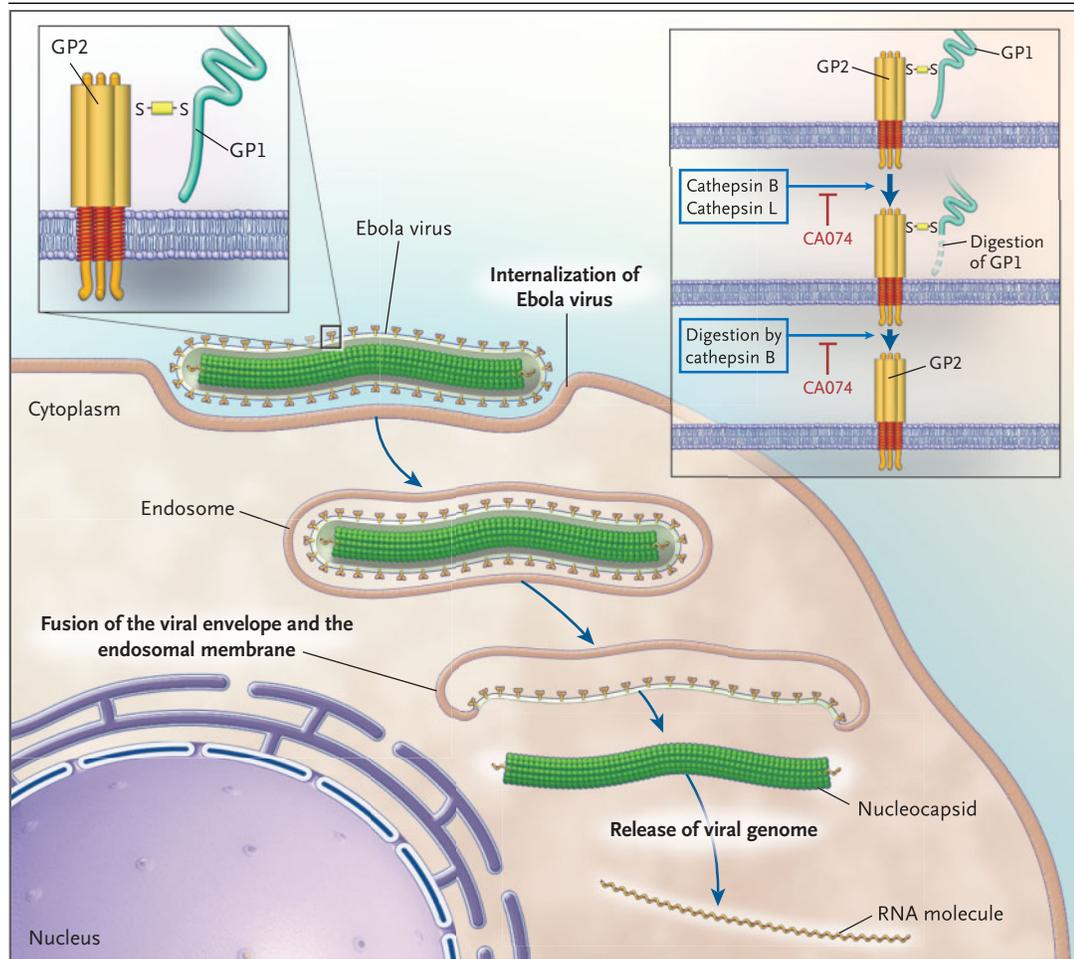


Figure 1. Entry of Ebola Virus into a Cell.

On binding to cell-surface receptors, Ebola virus is internalized and sequestered within an endosome. A recent study by Chandran and colleagues¹ shows that two endosomal proteases, cathepsin B and cathepsin L, then cleave the viral glycoprotein 1 (GP1) to yield a short N-terminal fragment, which is further digested by cathepsin B, leaving only GP2. Presumably, GP2 initiates fusion between the viral envelope and the endosomal membrane, leading to the release of the viral genome into the cytoplasm. A selective inhibitor of cathepsin B, CA074, inhibits the proteolysis of GP1, thereby preventing fusion and thus infection.

are toxic to cells and are therefore unlikely to be used in clinical settings, the development of new types of cathepsin inhibitors that might safely block the replication of Ebola virus in humans may offer a means of controlling this deadly infection.

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