Uncovering the mystery of Ebola virus entry: Lock and key

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How Ebola virus (EBOV) enters a host cell remains intriguingly mysterious to the public. Recently, a study led by George F Gao and his colleagues has unveiled how the primed glycoprotein on the envelope of EBOV binds to its endosomal receptor Niemann-Pick C1 (NPC1) molecule during the process of virus membrane fusion with the host cells, an essential step for viral entry (Wang et al., 2016). This fine resolution of the viral glycoprotein with NPC1 at the atomic level sheds light on the development of therapeutic inhibitors against EBOV infection.

After the unprecedented EBOV outbreak in West Africa in 2013–2014, the global efforts have consolidated to develop different kinds of vaccines and therapeutic drugs against EBOV. However, the evidence that EBOV can reside in the eyes and semen in convalescent patients suggests that the eradication of this virus is difficult, necessitating the development of an array of anti-viral therapeutic approaches. It also calls for better understanding of the molecular basis of EBOV infection and related pathogenesis.

Virus attachment and membrane fusion are the initial steps in the entry process. Many host cell attachment factors, such as C-type lectins, including DC-SIGN (dendritic cell-specific ICAM3-grabbing non-integrin; also known as CD209) and L-SIGN (liver and lymph node SIGN; also known as CLEC4M), and several cell surface proteins, including integrins, T cell immunoglobulin, and mucin domain-containing (TIM) proteins and tyrosine protein kinase receptor 3 (TYRO3) family members, are involved in EBOV attachment. The same team has also resolved the co-crystal structures of human TIM proteins complexed

with the ligand, phosphatidylserine (Wang et al., 2015)

When the EBOV attaches to the host cell membrane, it is “swallowed” by a macropinocytosis-like process, following which it traffics through the early and late endosomes. In the endosomes, the glycoprotein (GP) present on the envelope of EBOV is cleaved by cysteine enzymes (cathepsins B and L) of the host cells into a “primed” form, thereby exposing the receptor binding site to the endosomal receptor NPC1. NPC1 is a ubiquitously expressed protein with 13 trans-membrane domains residing mainly in the limiting membranes of the late endosomes and lysosomes. It functions to transport cholesterol with the help of a soluble NPC2 protein. EBOV licenses NPC1 molecule as the “key” to enter host cells. Since many years, virologists have been trying to understand the nature of the primed EBOV glycoprotein interacting with the NPC1 molecule.

Gao’s team spent three years to solve the crystal structure of the second luminal domain (domain C) of NPC1 molecule (NPC1-C), which is responsible for the binding of the primed EBOV glycoprotein. They showed that NPC1-C has a helical core structure surrounded by several β -strands, with two protruding loops. Furthermore, they determined the complex structure formed between the primed glycoprotein and NPC1-C. People can see for the first time that NPC1-C utilizes its two protruding loops to contact a hydrophobic cavity present on the top of the primed glycoprotein. Interestingly, one protruding loop deeply inserts into the cavity, analogous to a “key” being inserting into the hole of a “lock”. It is expected that future drug candidates can be designed to block the hole of this “lock”, to prevent virus infection. Scientists have found several NPC1-targeting compounds that can inhibit EBOV infection. However, these drug candidates caused severe side effects during

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clinical trials, attributable to the physiological roles of NPC1. This key-lock feature revealed in the Cell paper provides a new concept for designing drugs targeting the hole of “lock” in EBOV glycoprotein, in the hope to reduce toxicity.

In addition, a new membrane fusion mechanism has been proposed by the authors. They identified several conformational changes in the primed glycoprotein, upon enzymatic cleavage and after NPC1-C binding. The upward movement of a short helix in the $\beta 3$ - $\alpha 1$ loop of GP1 subunit likely helps to release the N-terminal portion of the IFL (internal fusion loop) in the GP2 subunit, which probably triggers the membrane fusion. The four major types of membrane fusion are as follows: (i) interaction of the fusion protein with a cell surface receptor; (ii) sequential interactions with a cell surface receptor and co-receptor(s); (iii) exposure to a low-pH environment in endosomes after being engulfed (e.g., endocytosis); and (iv) sequential interactions with a cell surface receptor followed by exposure to low-pH environment in endosomes. The new finding in the paper would propose a fifth fusion triggering mechanism, i.e., exposure

to a low-pH environment in the late endosomes before interaction with an endosomal receptor. As the Marburg virus also has a similar hydrophobic cavity on top of its primed glycoprotein and needs NPC1 for membrane fusion, this fusion triggering mechanism likely represents a unique feature of filoviruses.

On January 14, 2016, WHO declared the end of the Ebola outbreak in West Africa. One day later, a new case report of Ebola infection occurred in Sierra Leone. Such instances alarm the scientific community to invest more effort in eradicating the deadly virus.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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