Molecular basis of Ebola virus bound to its endosomal receptor NPC1

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research team led by Prof. George F Gao(高福) at the CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, uncovered the mystery of Ebola virus entry in the endosome of host cell, which was published in *Cell* (2016, 164(1—2): 258—68).

Ebola virus can cause a rapidly-lethal hemorrhagic fever in humans and primate animals, and at present no clinically-approved antiviral therapeutics are available. Since December 2013, a historically-unprecedented EBOV outbreak has occurred in the West Africa, causing more than 28,000 human infections and over 11,000 related deaths as of January 10th 2016. Under this urgent situation, it calls for great efforts to develop the vaccines and antiviral therapeutics, which needs a comprehensive and decent understanding of the pathogenesis and molecular basis of EBOV infection.

Regarding the infection by Ebola virus, the virus entry process includes two key steps, virus attachment on the cell membrane and virus membrane fusion in the endosome. Before they obtained the breakthrough in the study of Ebola virus entry in the endosome of the host cell, George F Gao's group had studied the host cell attachment factor, T cell immunoglobulin and mucin domain-containing (TIM) proteins, and elucidated the molecular basis of interaction between the TIM proteins and their ligand phosphatidylserine (PS), providing a structural insight into the Ebola virus enhancing infection by TIM proteins. This finding was published in a Chinese journal, *Chinese Science Bulletin*, as a cover story.

More excitingly, they solved 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 in the endosome. NPC1-C has a helical core structure surrounded by several β-strands, with two protruding loops. Furthermore, they determined the complex structure between the primed glycoprotein and NPC1-C. NPC1-C utilizes its two protruding loops to contact a hydrophobic cavity on the top of the primed glycoprotein. Interestingly, one protruding loop deeply inserts into the cavity, just like that one 'key' inserting into the hole of a 'lock'. It is expected that, in the nearing future, the drug candidates can be designed to block the hole of 'lock', and thus prevent the virus infection. Scientists have found several NPC1-targeting compounds that can inhibit the virus infection. However, these drug candidates had severe side effects in the clinical trials, attributable to the physiological roles of NPC1. This key-lock feature revealed in the *Cell* paper would enable a new designing concept in drugs targeting the hole of 'lock' in EBOV glycoprotein, in the hope to reduce the toxicity.

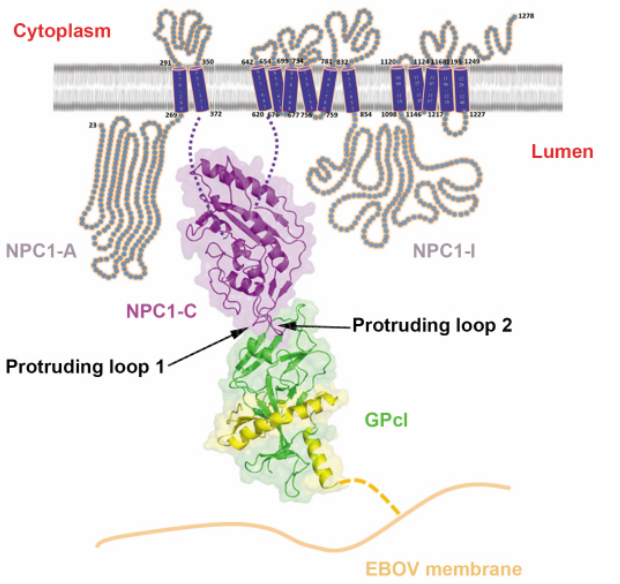

Figure Complex structure of the NPC1-C and the primed Ebola viral glycoprotein.