Protein Cell 2010, 1(5): 425–426
DOI 10.1007/s13238-010-0051-9

Protein & Cell

HIGHLIGHT

Return and reformation after a century — from 1918 to 2009 H1N1

Xiaoxue Zhang

Undoubtedly, H1N1 has been a keyword for the past year of 2009. This swine influenza virus is the first pandemic of the 21st century (announced by the World Health Organization (WHO) on June 11th, 2009) and took around 18,000 lives by April, 2010 (http://www.who.int/csr/don/2010_04_23a/en/index.html). Despite of the well-acknowledged high mutation rate for pandemic influenza viruses, the Wilson group at the Scripps Research Institute (Xu et al., 2010), the Stevens group at Centers for Disease Control and Prevention (Yang et al. 2010), and the Gao group at the Institute of Microbiology, Chinese Academy of Sciences (in the current issue of *Protein & Cell*) independently discovered that the 1918 and 2009 pandemic influenza viruses share fantastic similarities in regards to the structure of hemagglutinin (HA), which is the major influenza virus surface envelope protein. In addition, the Gao group also reported the changes of *N*-glycosylation sites in the HA protein and proposed another underlying evolutionary hint.

Influenza viruses are characterized by rapid gene segment exchanges (gene reassortment) that lead to highly frequent formation of new virus stains, causing resistance to vaccines raised against previous stains. HA is one of the 11 proteins encoded by influenza A. This antigenic glycoprotein is the main component on the surface of influenza virus particles, mediating virus recognition through interaction with sialic acid-containing receptors on the surface of mammalian cells and causing the fusion of the host endosomal membrane with the viral membrane to allow the entry of viral genome. There are 16 serotypes of HA (H1–16), among which three are found in human pandemics. Due to its significant roles in the viral life cycle, HA has high pathogenicity, and pandemic is often caused by introduction of a new HA serotype; also for these reasons, HA is essential for stimulating host neutralization-antibody responses and for developing flu vaccines. It is also a reassortment 'hot-spot' for influenza viruses to overcome antibody targeting. Generally, a seasonal influenza vaccine has little impact against similar virus stains within a few years, which makes it challenging to prevent and treat the flu.

Using an X-ray crystallography approach, the Wilson, Stevens and Gao group all found the HA heads (including five defined antibody recognizing epitopes, Sa, Sb, Ca1, Ca2 and Cb) from 1918 and 2009 H1N1 influenza viruses have strikingly similar shapes, which are both different from the H1 structures of seasonal strains. The common antigenic modules provide the molecular mechanism for the observations in another report: vaccine raised against 1918 H1N1 is able to protect mice from 2009 virus, and vice versa (Wei et al., 2010). This cross-reactivity also explains the facts that 2009 H1N1 is resistant to current vaccines against seasonal flu, and that 2009 H1N1 has higher infectivity for younger people than older ones, who are generally believed to be more vulnerable to influenza viruses.

These structural similarities may be due to a common origin. The HA proteins from 1918 and 2009 H1N1 viruses are both believed to originate from swine (the 2009 H1N1 is referred to as swine-origin influenza virus (S-OIV)), and the two stains show high similarity on encoding sequence as well as pathogenesis. Why is the HA protein well preserved in swine yet highly variable in human? Scientists proposed a possibility that swine have much shorter life spans than humans, which gives less time for swine to develop an immune system as sophisticated as in humans. This, in turn, puts lower pressure for the virus to change. However, further knowledge about the immune system in swine is required to prove this hypothesis.

Despite the high structural similarity, the 2009 H1 protein shows obvious differences in comparison to the 1918 H1. One difference is in *N*-glycosylation. Evolution of new *N*-glycosylation sites is a common strategy for influenza virus to develop resistance to antibodies because sugars from the host cells can attach to the glycosylation sites and potentially mask antibody recognition. The Gao group reported that the arrangement of *N*-glycosylation sites in 2009 H1 is different from those in seasonal flu viruses and in 1918 H1N1. They revealed an extra *N*-glycosylation site near the second basic patch region, which is a defined structural module initially found in the 1918 H1 structure and has important roles in membrane fusion and infection. The novel *N*-glycosylation site in 2009 H1 may reduce the interaction of basic enzymes

with the basic patch and may also interfere with antibody recognition.

Moreover, the Gao group found that the basic patch region in 2009 H1 is larger than that in other H1 proteins, including 1918 H1. It is believed that the infectivity of the influenza virus is enhanced by a stronger basic patch. These discoveries further explain why the 2009 H1N1 lacks cross-antigenicity with seasonal influenza viruses and is able to escape the attack of previously available antibodies. Furthermore, the additional *N*-glycosylation site and larger basic patch indicate that the 2009 H1N1 protein has undergone evolutionary changes despite of high structural similarity with 1918 H1N1. These changes potentially provide a 'path' for the virus to escape the antibody recognition and enhance its virulence. However, the functional significance for these changes are yet to be further determined.

One question is whether 2009 H1N1 will follow the path of 1918 virus, which continued to circulate till mid-1950s. The antigenic similarity may be helpful to establish protection approaches for the descendants of 2009 H1N1 in future pandemics, while the changes in H1 glycosylation and basic patches have to be taken into consideration.

REFERENCES

Wei, C.J., Boyington, J.C., Dai, K., Houser, K.V., Pearce, M.B., Kong, W.P., Yang, Z.Y., Tumpey, T.M., and Nabel, G.J. (2010). Cross-neutralization of 1918 and 2009 influenza viruses: role of glycans in viral evolution and vaccine design. Sci Transl Med 2, 24ra21.

Xu, R., Ekiert, D.C., Krause, J.C., Hai, R., Crowe, J.E., Jr., and Wilson, I.A. (2010). Structural basis of preexisting immunity to the 2009 H1N1 pandemic influenza virus. Science 328, 357–360.

Yang, H., Carney, P., and Stevens, J. (2010). Structure and receptor binding properties of a pandemic H1N1 virus hemagglutinin. PLoS Curr Influenza RRN1152.

Zhang, W., Qi, J., Shi, Y., Li, Q., Gao, F., Sun, Ye., Lu, Xi., Lu, Q., Vavricka, C.J., Liu, D., *et al*. (2010). Crystal structure of the swine-origin A (H1N1) — 2009 influenza A virus hemagglutinin (HA) reveals similar antigenicity to that of the 1918 pandemic virus. Protein Cell 1.

