Researchers Reveal the Molecular Basis of the Broad Neutralizing Activity of Human Antibody 3E1 against Influenza A Viruses

On Dec. 2nd, 2016, a joint team revealed online in *Nature Communications* that 3E1 could neutralize H1 and H5 subtype viruses by targeting a conserved and unique epitope on hemagglutinin (HA) stem region, hence inhibiting low pH-induced HA conformational change and blocking membrane fusion. Titled "Human antibody 3E1 targets the HA stem region of H1N1 and H5N6 influenza A viruses", this paper resulted from a collaborative research led by Prof. DING Jianping from the National Center for Protein Science Shanghai, Center for Excellence in Molecular Cell Science, Shanghai Institute of Biochemistry and Cell Biology, Shanghai

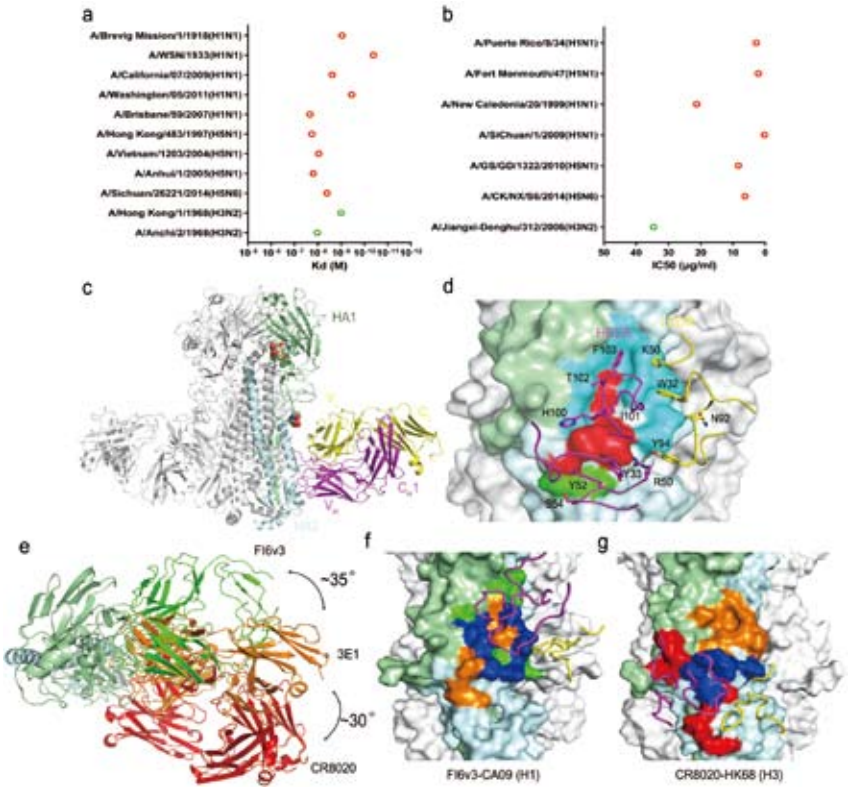

Figure 1. 3E1 neutralizes H1 and H5 subtype viruses, targeting a unique epitope of the HA stem region. (a). 3E1 binds to HAs of H1 and H5 subtype viruses. (b). 3E1 neutralizes H1 and H5 subtype viruses *in vitro*. (c). 3E1 recognizes a unique epitope of the HA stem region. (d). The 3E1 epitope comprises part of the F subdomain (cyan), the fusion peptide (red) and the outmost *β*-stand (green). (e). The approach angle of 3E1 is in the middle of Type I and Type II bnmAbs. (f). The 3E1 epitope overlaps over 50 % (blue) with Type I bnmAbs. (g). 3E1 epitope overlaps over 50 % (blue) with Type II bnmAbs.

Institutes for Biological Sciences, Chinese Academy of Science (CAS), Prof. SUN Bing from the Institut Pasteur of Shanghai, CAS and Prof. CHEN Hualan from the Harbin Veterinary Research Institute.

Influenza remains a grave and persistent threat to human health, while imposing a heavy economic burden on patients and countries worldwide. Influenza epidemics recur yearly and cause 3~5 million cases of severe illness and 0.25~0.5 million deaths worldwide annually. To date, vaccination remains the most effective measure to control infection, and antiviral drugs are also available to treat influenza at the early stage of infection. However, the development of more effective antiviral drugs, therapeutic monoclonal antibodies and vaccines that can provide broad protective activities is urgently needed to prevent and treat continually emerging novel influenza viruses. Hemagglutinin (HA) is the main target of most neutralizing antibodies, and recent studies showed that antibodies targeting the conserved HA stem region could be more cross-reactive.

In the past years, Prof. DING Jianping's group has carried out the structural and functional studies of a number of antibody drugs in complexes with their targets. Recently, Prof. SUN Bing's group extracted several broadly neutralizing monoclonal antibodies. To reveal the molecular basis of the broad neutralizing activity of these antibodies, Ph.D. candidate WANG Wenshuai from Prof. Ding's group carried out the structural and functional studies of the broadly neutralizing monoclonal antibody 3E1in collaboration with colleagues from Profs. SUN Bing and CHEN Hualan's groups.

They found that 3E1 exhibited broad neutralizing activity against H1 and H5 subtype viruses *in vitro* and protected mice against H1N1 and H5N6 viruses *in vivo* by inhibiting the low pH-induced HA conformational rearrangement, hence blocking membrane fusion. The crystal structures of 3E1 Fab in complex with the HA protein of two H1N1 strains showed that both the heavy and light chains of 3E1 recognize a conserved conformational epitope comprising the C-terminus of the fusion peptide, part of the F subdomain and the C-terminus of the outermost β-strand preceding helix A. The epitope of 3E1 is comprised of the major parts of the epitopes recognized by all previously identified broadly neutralizing monoclonal antibodies, and thus represents a unique epitope. The structural and biological data suggest the potential of 3E1 as a therapeutic drug against H1 and H5 subtype viruses, and shed some light on the design of more effective antiviral drugs and potential universal vaccines against influenza A viruses.

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