CLINICAL IMPLICATIONS OF BASIC RESEARCH

Stalking Influenza Diversity with a Universal Antibody

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The back-and-forth battle between influenza viruses and humans is defined by diversity. We fight previously unseen pathogens with a diverse repertoire of antibodies, and influenza viruses evade our immune system by presenting us with diverse surface-protein sequences. Corti and colleagues[1] have recently discovered a universal influenza antibody, revealing an Achilles' heel common to all influenza strains that we can now target with next-generation antiviral drugs and vaccines.

The current countermeasures against seasonal influenza are the use of annual vaccines and antiviral drugs, such as oseltamivir. Seasonal strains (presently, H1N1, H3N2, and B type) evade our immune systems after vaccination or previous infection by constantly changing the structure of their hemagglutinin (HA) surface protein. As a result, we cannot eradicate seasonal influenza, which causes about 600 million infections and 400,000 deaths worldwide annually.

Making matters worse, diverse influenza viruses — containing HA proteins of 16 distinct antigenic subtypes (H1 to H16) — circulate globally in wild aquatic birds (and to a lesser extent in pigs and horses) and may someday mix together and mutate into a pandemic virus. The 1918 "Spanish flu" pandemic contributed to 20 million to 50 million deaths worldwide. Avian H5N1 influenza viruses that are endemic in Egypt and Indonesia have a case fatality rate of approximately 60% in humans but, fortunately, have not yet gained the ability for sustained human-to-human spread.

The holy grail in the influenza field is a universal vaccine, but do the HA proteins of all influenza strains have a common epitope to target? To answer that question, Corti et al. screened 104,000 peripheral-blood plasma cells from eight recently infected or vaccinated donors for antibodies that recognize each of three diverse influenza strains: H1N1 (swine-origin influenza) and H5N1 and H7N7 (highly pathogenic avian influenzas) (Fig. 1). From one donor, they isolated four plasma cells that produced an identical antibody, which they called FI6. This antibody binds all 16 HA subtypes, neutralizes infection, and protects mice and ferrets from lethal infection. The most broadly reactive antibodies that had previously been discovered recognized either one group of HA subtypes or the other,[2,3] highlighting how remarkable FI6 is in its ability to target the gamut of influenza subtypes.

To see how FI6 hits the bull's-eye of this moving target, they determined the crystal structure of the antibody when it was bound to H1 and H3 HA proteins. Sitting atop the HA spike is a globular head domain that binds to cellular receptors during viral entry and contains the major antigenic sites targeted by the immune system. Because of this selective pressure, the sequence in the head domain drifts enough to require an updated seasonal vaccine most years. A stalk domain connects the head to the viral membrane and is responsible for fusing viral and host cell membranes so that the pathogen can invade human cells. The immune system usually does not have a strong response to the partially hidden stalk domain, so portions of the stalk remain highly conserved across all influenza subtypes. The FI6 antibody makes extensive contacts with conserved parts of the stalk, thereby blocking HA from harpooning a sticky fusion peptide into the host membrane during viral entry.

The discovery of FI6 provides us with a broadly neutralizing antibody that recognizes all 16 HA subtypes, including emerging ones, such as H5N1. As such, FI6 could prove invaluable in controlling prepandemic and early pandemic outbreaks. Because the replication of the influenza virus is somewhat error-prone, the virus evolves as a quasispecies, and widespread use of antiviral drugs can lead to resistant strains. Such has been the case for oseltamivir and for the M2 ion channel blocker amantadine. Therefore, before

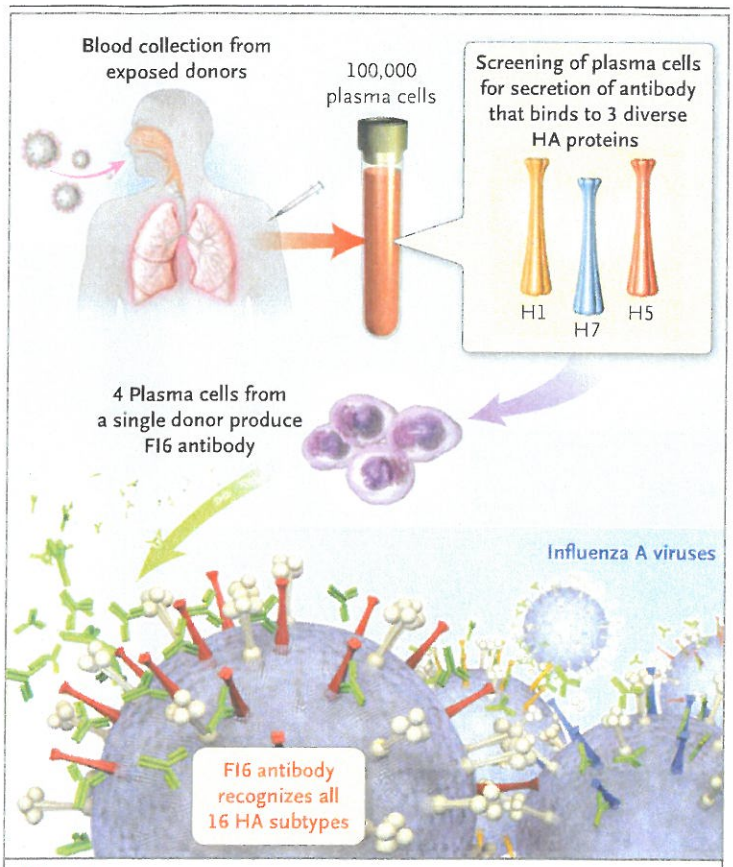

Figure 1. A Universal Influenza Antibody.

Diverse influenza A viruses have 16 hemagglutinin (HA) subtypes (H1 to H16) belonging to group 1 or group 2. Searching for a broadly neutralizing antibody, Corti et al.[1] collected blood from eight previously infected or vaccinated donors. Then, they screened about 100,000 plasma cells for an antibody that binds HA subtypes in group 1 (H1 and H5) and group 2 (H7). Four cells from a single donor produced the FI6 antibody, which recognized all 16 HA subtypes and protected mice and ferrets from lethal infection. FI6 targets HA's stalk, binding to a large conserved footprint while avoiding peripheral deviations.

considering FI6 as a long-term prophylactic or therapeutic agent against seasonal influenza, we would first have to determine whether the influenza virus could quickly mutate the epitope targeted by FI6 and escape recognition by FI6 after exposure.

A more important clinical implication of this work is the identification of a universal neutralizing epitope in the HA stalk at the atomic level, an important intellectual landmark for the development of a universal influenza vaccine. In the absence of the immunodominant head domain, isolated portions of the HA stalk that include the FI6 epitope have already been shown to stimulate broad, but not universal, protective effects against H1N1 and H3N2 strains in vaccinated animals.[4,5] Using protein engineering and adjuvants to focus the immune system on the FI6 epitope may be the critical next step along the path to a universal vaccine.

Why does not repeated exposure to diverse HA antigens of various subtypes protect humans against seasonal and pandemic infections? Some observers think that the presence of the immunodominant head domain may skew secondary responses away from the stalk. If so, the question arises as to whether persons who have been infected with current strains or vaccinated against them will have a harder time mounting a universal response than those who are immunologically naive. Basic and clinical studies have now identified broadly neutralizing stalk-binding antibodies in only a few subjects, which raises the question of whether most humans are capable of generating broadly neutralizing antibodies, such as FI6. Finally, if the FI6 epitope is susceptible to sequence drift similar to the head domain, will we also have to reformulate universal vaccines? Although the task of obtaining a universal vaccine is daunting, the discovery of a universal antibody is a monumental first step.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Corti D, Voss J, Gamblin SJ, et al. A neutralizing antibody selected from plasma cells that binds to group 1 and group 2 influenza A hemagglutinins. Science 2011;333:850-6.
2. Sui J, Hwang WC, Perez S, et al. Structural and functional bases for broad-spectrum neutralization of avian and human influenza A viruses. Nat Struct Mol Biol 2009;16:265-73.
3. Ekiert DC, Friesen RHE, Bhabha G, et al. A highly conserved neutralizing epitope on group 2 influenza A viruses. Science 2011;333:843-50.
4. Steel J, Lowen AC, Wang TT, et al. Influenza virus vaccine based on the conserved hemagglutinin stalk domain. MBio 2010;1(1):pii:e00018-10.
5. Bommakanti G, Citron MP, Hepler RW, et al. Design of an HA2-based Escherichia coli expressed influenza immunogen that protects mice from pathogenic challenge. Proc Natl Acad Sci U S A 2010;107:13701-6.