CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Toward a universal influenza vaccine: from the perspective of protective efficacy

Clin Exp Vaccine Res 2013;2:71-73
http://dx.doi.org/10.7774/cevr.2013.2.2.71
pISSN 2287-3651 • eISSN 2287-366X

Yo Han Jang[1], Baik Lin Seong[1,2]
[1]Laboratory of Molecular Medicine, Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul; [2]Translational Research Center for Protein Function Control, Yonsei University, Seoul, Korea

Received: March 26, 2013
Revised: April 5, 2013
Accepted: April 15, 2013

Corresponding author: Baik Lin Seong, PhD
Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-749, Korea
Tel: +82-2-2123-2885, Fax: +82-2-362-7265
E-mail: blseong@yonsei.ac.kr.

No potential conflict of interest relevant to this article was reported.

Influenza viruses continue to take a heavy toll on public health worldwide. Despite prior infections or vaccinations, a hugely variable nature of the viruses (antigenic drift) and the frequent exchange of genetic materials among different strains (antigenic shift) leave the most human population vulnerable to subsequent infections. In particular, antigenic shift occasionally gives rise to a novel virus to which most human population has little pre-exiting immunity, causing a fatal damage to human health globally, as seen in past pandemics [1].

To be better prepared for influenza infections, considerable efforts have been made to develop a universal vaccine that provides a broad-spectrum protection against a variety of influenza viruses. While the strain-specific protection of a vaccine heavily relies on the hemagglutinin (HA)-inhibitory or viral-neutralizing antibodies that block the attachment of the HA of the virus to the host receptors (sialic acids), this is not a reliable approach to design a universal vaccine, especially because the globular head domain of the HA is considerably variable and therefore can easily escape from neutralization by pre-existing antibodies. It is not surprising that recent major advancements in the development of universal vaccine were made by the identifications of more conserved domains in surface antigens such as HA and M2 ion channel and by the discoveries of their responding antibodies *in vivo* [2,3]. As a consequence, the HA stalk domain and the external domain of the M2 (M2e) have been extensively studied as attractive targets for a universal vaccine. Either as recombinant proteins or as synthetic small peptides, these conserved regions were used as immunogens to elicit broad-spectrum humoral responses. Alternatively, monoclonal antibodies (mAb) directed to the domains were evaluated for protective or therapeutic efficacy in passive immunization [3-5]. Whether through direct neutralization of virus or by associated mechanisms of virus clearance such as the antibody-dependent cell-mediated cytotoxicity or complement cascade resulting in cytolysis, these antibodies were shown to elicit broadly neutralizing effects against distinct viral subtypes in several animal models, establishing the proof-of-concept for the design of a universal vaccine. However, their protective efficacy were generally weak or short-lived compared to classical inactivated or live attenuated influenza vaccines (LAIV), providing only partial protection against lethal infections [3-5]. This still leaves the development of a long-lasting and protective universal vaccine a real challenge. The mAbs to viral conserved domains may be better suited for therapeutic than prophylactic purposes, and despite high cost, would have undisputed benefits for high-risk groups, such as the elderly and immunocompromised, and against life-threatening influenza infections. Recombinant

proteins or synthetic peptides engineered to contain only the HA stalk region appear to hardly confer sufficient protection against infection due to the lack of 'gold standard' epitopes of the HA globular head domain. This led to a cocktail vaccine strategy combining the classical seasonal vaccine with the universal vaccine [6]. Such a vaccine formulation is likely to provide strain-specific protection against a matching strain as well as mitigating severe infection by drifted or newly emerged viruses.

Because of the highly variable nature of RNA viruses and relatively weak immunodominance of the conserved regions of viral proteins, the development of a universal influenza vaccine that ideally confers sufficient protection against all subtypes does not appear achievable within the near future. However, the availability of reverse genetics for influenza virus and better understanding on immune system open a wide range of possibilities of designing more broadly protective universal vaccine than they are now. If a previous strain-specific vaccine is rationally redesigned to efficiently present the antigen, for example the conserved regions in the HA stalk domain, to the immune system, the vaccine would remain protective against the matching strain and, at the same time, confer higher level of cross-protection against other strains. Such a strategy may be more difficult for inactivated or live attenuated vaccines than for recombinant protein vaccines because the modification of viral proteins occasionally leads to the loss of viral viability, limiting the production of the vaccines. LAIV nevertheless presents potential advantages over non-live vaccine modalities. Closely mimicking natural infection, the LAIV was shown to be able to stimulate all phases of immune responses including humoral and cell-mediated immunity, both systemically and locally. In particular, the LAIV delivers conserved internal proteins such as NP, M1, NS1, and polymerase complexes (PB1, PB2, and PA), to be processed and presented to cytotoxic T cells, conducive to broad heterosubtypic protection. In addition to the intrinsic cytotoxic T-lymphocyte-mediated cross-protection, the LAIV could be appropriately modified such that the HA stalk domains are processed and become more accessible to B cell receptors for antibody generation, one step closer to becoming a protective universal vaccine. Relevant to this expectation is the observation that natural infection or vaccination with the 2009 pandemic H1N1 virus, unlike those with seasonal influenza viruses, preferentially induced broadly neutralizing antibodies [7-9], which is auspicious for the design of cross-protective LAIV. More efforts should be dedicated to further identifying the conserved, yet unknown, epitopes of influenza viral proteins, not only on HA but neuraminidase (NA) as well. This would allow a wider choice of targets and strategies towards developing a universal vaccine. It is also possible that there exists potential cryptic epitopes in HA and NA that have been kept dormant and conserved because of the lack of immune selection during an influenza infection. The reverse genetic platform now allows not only the testing of the potential existence of such cryptic epitopes but also the 'activation' of the epitopes by antigen presenting cells, eliciting cross-protective responses to various influenza viruses.

From the perspective of protection, vaccine strategies based only on the induction of antibodies to conserved regions in viral proteins should be applied with great caution since the broad protection are usually short-lived and the protection is compromised as compared to currently licensed vaccines. An ideal universal vaccine, therefore, should ultimately stimulate all the arms of immune responses that are directed not only to the conserved but also to the variable regions in surface antigens, as well as to the internal T-cell epitopes. Combining the cross-protective nature of LAIV with an efficient presentation of conserved epitopes, either pre-existing yet cryptic because of a lack of immune selection, will remain the major task in the rational design of a truly universal vaccine.

References

1. Neumann G, Noda T, Kawaoka Y. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Nature 2009;459:931-9.
2. Ekiert DC, Bhabha G, Elsliger MA, et al. Antibody recognition of a highly conserved influenza virus epitope. Science 2009;324:246-51.
3. Neirynck S, Deroo T, Saelens X, Vanlandschoot P, Jou WM, Fiers W. A universal influenza A vaccine based on the extracellular domain of the M2 protein. Nat Med 1999;5:1157-63.
4. Wang TT, Tan GS, Hai R, et al. Vaccination with a synthetic peptide from the influenza virus hemagglutinin provides protection against distinct viral subtypes. Proc Natl Acad Sci U S A 2010;107:18979-84.
5. 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.
6. Sommerfelt MA. T-cell-mediated and humoral approach-

es to universal influenza vaccines. Expert Rev Vaccines 2011;10:1359-61.
7. Wrammert J, Koutsonanos D, Li GM, et al. Broadly cross-reactive antibodies dominate the human B cell response against 2009 pandemic H1N1 influenza virus infection. J Exp Med 2011;208:181-93.
8. Jang YH, Byun YH, Lee YJ, Lee YH, Lee KH, Seong BL. Cold-adapted pandemic 2009 H1N1 influenza virus live vaccine elicits cross-reactive immune responses against seasonal and H5 influenza A viruses. J Virol 2012;86:5953-8.
9. Lee KH, Seo SU, Song JM, Lee CM, Kim HA, Seong BL. Characterization of live influenza vaccine donor strain derived from cold-adaptation of X-31 virus. Vaccine 2006; 24:1966-74.