CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Challenges in the development of T-cell–based universal influenza vaccines

Clin Exp Vaccine Res 2017;6:1-3
https://doi.org/10.7774/cevr.2017.6.1.1
pISSN 2287-3651 • eISSN 2287-366X

Jung-Ok Kang, Jun Chang
Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul, Korea

Received: December 15, 2016
Revised: December 30, 2016
Accepted: January 10, 2017

Corresponding author: Jun Chang, PhD
Graduate School of Pharmaceutical Sciences, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 03760, Korea
Tel: +82-2-3277-2549, Fax: +82-2-3277-3051
E-mail: tcell@ewha.ac.kr

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

KVS KOREAN VACCINE SOCIETY

An influenza virus infection generates humoral and cellular immunity that provides protection against reinfection if it does not subvert an infected host. The efficacy of current influenza vaccines depends on humoral immunity directed at surface glycoproteins, such as hemagglutinin and neuraminidase. The antibody-mediated protection is effective against homologous strains but not against heterologous strains with serologically distinct surface proteins. The highly mutagenic properties of influenza viral RNA polymerase and immunologic pressure from the host result in strains with antigenic drifts mainly in those glycoproteins, which reduce or eliminate a vaccine's efficacy. Thus, vaccine formulations must be updated annually through surveillance of strains that will most likely be prevalent in the subsequent flu season. However, as demonstrated by previous epidemics and pandemics, there have been years in which flu vaccines were ineffective owing to discrepancies between the strains used to create the vaccines and the strains that ended up circulating or the emergence of a new strain as a result of antigenic drift and accumulated mutations or antigenic shift by genetic reassortment between different viral subtypes. Moreover, it takes several months to isolate and amplify new strains and create vaccines against them. These limitations of current vaccines spur the need to develop new vaccines capable of protecting against a broad range of influenza strains.

Such broadly protective "universal influenza vaccines" are based on the phenomenon of heterosubtypic immunity, wherein host immune responses to highly conserved epitopes across several influenza subtypes confer protection against heterosubtypic challenge. In animal models, it has been shown that heterosubtypic immunity could be mediated by T cells, specifically CD8+ T cells and CD4+ T cells [1,2]. The heterosubtypic T cells are cross-reactive to conserved peptides, predominantly those of internal viral proteins such as polymerase-binding protein (PB) 1, matrix 1 (M1), and nucleoprotein (NP). CD8+ T cells are thought to be the primary effectors of heterosubtypic immunity owing to their cytotoxic effects against virus-infected cells and antiviral suppressor function. In contrast, the role of CD4+ T cells in mediating heterosubtypic immunity is less clear, but it is an increasing focus of attention [3,4]. Recent studies suggest that heterosubtypic CD4+ T cells mediate cross-protection through various mechanisms, including direct cytolytic activity and interactions with B cells or CD8+ T cells [4-6]. In humans, recognition by CD4+ T cells and CD8+ T cells of conserved epitopes in internal proteins was shown to correlate with protection against influenza infection [7-9]. Regarding protection against influenza, lung resident memory T cells (T_{RM}), which are present locally in the airways or parenchyma of the respiratory tract, are receiving

increasing attention. Recent studies have shown that lung T_{RM} cells have superior protective capacity as compared to circulating memory CD8+ T cells [10,11]. Lung T_{RM} cells have also been found in humans, and it has been suggested that they can respond to influenza infection [12,13]. However, a direct connection between T_{RM} cells and reduced disease severity in humans remains to be made.

Overall, recent studies strongly suggest that T-cell–based vaccines could be a promising strategy for a "universal influenza vaccine." However, there are some challenges facing development of a T-cell–based universal influenza vaccine. One is generation of durable antigen-specific memory responses in the respiratory tract. Regarding this, previous studies have shown that several factors such as dendritic cells in the respiratory tract, antigen persistence in the lungs, and antigen delivery routes might be associated with generation of long-lasting T_{RM} cells in the lungs [14-16]. Another challenge lies in developing vaccines that provide sufficient coverage to individuals with diverse HLA haplotypes, which presents the need to examine T-cell responses in the context of ethnicity. There are also concerns about inflammatory pathologies which could be promoted and/or exacerbated by vaccine-induced T cells. In addition, the correlation between vaccine-induced T-cell responses and protection is difficult to measure quantitatively in humans, which presents another barrier to developing T-cell–based influenza vaccines. Despite these obstacles, it is expected that our growing understanding of the mediators of heterosubtypic immunity and technological advancements related to vaccine design will expedite the development of T-cell–based, broad-acting, new influenza vaccines.

ORCID

Jung-Ok Kang *http://orcid.org/0000-0002-4927-3195*
Jun Chang *http://orcid.org/0000-0002-8423-5987*

References

1. Liang S, Mozdzanowska K, Palladino G, Gerhard W. Heterosubtypic immunity to influenza type A virus in mice: effector mechanisms and their longevity. J Immunol 1994; 152:1653-61.
2. Epstein SL. Control of influenza virus infection by immunity to conserved viral features. Expert Rev Anti Infect Ther 2003;1:627-38.
3. Swain SL, Agrewala JN, Brown DM, et al. CD4+ T-cell memory: generation and multi-faceted roles for CD4+ T cells in protective immunity to influenza. Immunol Rev 2006; 211:8-22.
4. Brown DM, Dilzer AM, Meents DL, Swain SL. CD4 T cell-mediated protection from lethal influenza: perforin and antibody-mediated mechanisms give a one-two punch. J Immunol 2006;177:2888-98.
5. Brown DM, Lee S, Garcia-Hernandez Mde L, Swain SL. Multifunctional CD4 cells expressing gamma interferon and perforin mediate protection against lethal influenza virus infection. J Virol 2012;86:6792-803.
6. McKinstry KK, Strutt TM, Kuang Y, et al. Memory CD4+ T cells protect against influenza through multiple synergizing mechanisms. J Clin Invest 2012;122:2847-56.
7. Lee LY, Ha DL, Simmons C, et al. Memory T cells established by seasonal human influenza A infection cross-react with avian influenza A (H5N1) in healthy individuals. J Clin Invest 2008;118:3478-90.
8. Wilkinson TM, Li CK, Chui CS, et al. Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. Nat Med 2012;18:274-80.
9. Sridhar S, Begom S, Bermingham A, et al. Cellular immune correlates of protection against symptomatic pandemic influenza. Nat Med 2013;19:1305-12.
10. Wu T, Hu Y, Lee YT, et al. Lung-resident memory CD8 T cells (TRM) are indispensable for optimal cross-protection against pulmonary virus infection. J Leukoc Biol 2014; 95:215-24.
11. McMaster SR, Wilson JJ, Wang H, Kohlmeier JE. Airway-resident memory CD8 T cells provide antigen-specific protection against respiratory virus challenge through rapid IFN-gamma production. J Immunol 2015;195:203-9.
12. Purwar R, Campbell J, Murphy G, Richards WG, Clark RA, Kupper TS. Resident memory T cells (T(RM)) are abundant in human lung: diversity, function, and antigen specificity. PLoS One 2011;6:e16245.
13. Piet B, de Bree GJ, Smids-Dierdorp BS, et al. CD8(+) T cells with an intraepithelial phenotype upregulate cytotoxic function upon influenza infection in human lung. J Clin Invest 2011;121:2254-63.
14. Zammit DJ, Turner DL, Klonowski KD, Lefrancois L, Cauley LS. Residual antigen presentation after influenza virus infection affects CD8 T cell activation and migration. Immunity 2006;24:439-49.
15. Kim TS, Gorski SA, Hahn S, Murphy KM, Braciale TJ. Dis-

tinct dendritic cell subsets dictate the fate decision between effector and memory CD8(+) T cell differentiation by a CD24-dependent mechanism. Immunity 2014;40:400-13.
16. Uddback IE, Pedersen LM, Pedersen SR, et al. Combined local and systemic immunization is essential for durable T-cell mediated heterosubtypic immunity against influenza A virus. Sci Rep 2016;6:20137.