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Commentary

"Universal Flu Vaccine": Can NK Cell-mediated ADCC Tip the Scales?

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The last century has witnessed incredible progresses in the control of infectious diseases. However, respiratory pathogens continue to threaten humans and cause serious public health and economic problems. Not only emerging pathogens but also viruses that have been known for a while continue to cause widespread issues (Summary analysis of 2014 survey of National Influenza Centres in the WHO Global Influenza Surveillance and Response System, 2014). Despite the relative efficacy of the inactivated vaccine against influenza A viruses (IAV) has been shown for many years, this virus is still responsible for seasonal widespread morbidity and mortality. These outbreaks are usually associated with mild symptoms but can also result in 3 to 5 million cases of severe illnesses, especially amongst elderly and young children. Influenza virus still accounts for 250,000 to 500,000 deaths each year during epidemic episodes (Summary analysis of 2014 survey of National Influenza Centres in the WHO Global Influenza Surveillance and Response System, 2014). This is due to the continuous antigenic drift that leads to vaccine mismatch and therefore negatively impacts on its effectiveness (Krammer and Palese, 2015). Moreover, more sporadically, pandemics due to highly virulent strains or transversal infections of animal strains to humans represent another important threat (Palese, 2004). In this context, it is of the utmost importance to urgently develop universal influenza vaccines. Current vaccines are yearly updated on the basis of the circulating strains but unfortunately mainly generate neutralizing antibodies (Abs) directed against epitopes contained in highly variable regions (Gerdil, 2003). Nevertheless pre-clinical studies have demonstrated promising data through the generation of neutralizing Abs against conserved regions such as the helix-A of the surface glycoprotein hemagglutinin (HA) (Eggink et al., 2014) but these observations have not yet been translated into humans.

Amongst additional functions triggered by Abs, Ab-dependent cellular cytotoxicity (ADCC) mediates antiviral activities through the binding of cell surface Ags by IgG subtypes on target cells. This ultimately leads to the lysis of the target cells by secreted lytic enzymes from effector cells. This secretion follows the recognition of Fc region of surface bound Abs by FcγRIIIα (CD16)-expressing cytotoxic effector cells from both innate and adaptive immunity such as Natural Killer (NK) cells or $CD8^+$ T cells. ADCC directed against IAV has been recognized for a long time(Jegaskanda et al., 2014). Since this class of Abs can target much more conserved proteins, understanding ADCC mechanisms during IAV infection might help in the development of universal influenza vaccines. For instance, a vaccine trial in HIV patients has been demonstrated protective in part through ADCC-mediating Abs(Madhavi et al., 2012).

In this issue, Vanderven and colleagues evidence in human samples from healthy influenza-exposed adults or symptomatic donors the existence of IAV-specific Abs capable of ADCC activity through NK cells (Vanderven et al., 2016). Interestingly these opsonizing Abs are directed against the highly conserved internal viral proteins nucleoprotein (NP) and matrix 1(M1) (~90% of identity in amino acid sequences between strains) from two different strains of IAV (H1N1/2009pdm and H3N2/2005). An increase for such cross-protective Abs was found in sera of naturally IAV-exposed humans suggesting that this class of Abs can potentially mediate heterologous response to various IAV strains during active infection. However, authors failed to detect rise in NK cell-mediated ADCC activity in volunteers experimentally exposed to IAV (H3N2/2005). The reasons for such a discrepancy are currently unknown. It is possible that the route/dose of infection as well as the strain used matters in the development of NK cell activating Abs. Other clinical studies investigating the contribution of these parameters will be informative to answer this question.

The presence and functionality of NP- and M1-specific NK cell-mediated ADCC in animal models including non-human primates has already been demonstrated (Jegaskanda et al., 2014). From a mechanistic point of view, the relevance of ADCC mediated against internal proteins remains puzzling. Given that NP and M1 are only minimally exposed at the cell surface during IAV life cycle, it will be important to determine the precise molecular/cellular mechanisms underlying NK cell-mediated ADCC. Although these Abs could mediate direct protection through opsonization of infected/dying cells, another explanation might involve

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indirect mechanisms (e.g. cytokine production or immune complex formation) that could lead to enhanced immune responses.

The origin of this class of Abs is currently unknown. Do they arise from specific B cell subsets? As suggested in this study, it is tempting to answer in the affirmative. Actually while most of the donors (healthy influenza-exposed and symptomatic) presented detectable levels of persistent NP- and M1-specific ADCC-mediating Abs, authors failed to concomitantly detect classical neutralizing Abs. Therefore, it will be important to understand the mechanisms and B cell populations involved in the generation of cross-reactive Abs.

For a long time, immunologists have focused their attention on the sole role of neutralizing Abs for vaccination efficacy. It is now clear that other Ab-dependent mechanisms can play relevant biological functions. The existence and persistence of Abs capable of NK cell-mediated ADCC against conserved viral proteins in patients with IAV infection is an important step in our comprehension of the immune responses against these viruses. This observation and their recognized relevance in experimental models of IAV infection should encourage a better investigation of ADCC-mediating Abs as a putative predictive parameter in vaccine efficacy and could further support the development of a "Universal influenza vaccine".

References

Eggink, D., Goff, P.H., Palese, P., 2014. Guiding the immune response against influenza virus hemagglutinin toward the conserved stalk domain by hyperglycosylation of the globular head domain. J. Virol. 88 (1), 699–704.

Gerdil, C., 2003. The annual production cycle for influenza vaccine. Vaccine 21 (16), 1776–1779.

Jegaskanda, S., Reading, P.C., Kent, S.J., 2014. Influenza-specific antibody-dependent cellular cytotoxicity: toward a universal influenza vaccine. J. Immunol. 193 (2), 469–475.

Krammer, F., Palese, P., 2015. Advances in the development of influenza virus vaccines. Nat. Rev. Drug Discov. 14 (3), 167–182.

Madhavi, V., Kent, S.J., Stratov, I., 2012. HIV-specific antibody-dependent cellular cytotoxicity: a novel vaccine modality. Expert. Rev. Clin. Immunol. 8 (8), 767–774.

Palese, P., 2004. Influenza: old and new threats. Nat. Med. 10 (12 Suppl), S82–S87.

Summary analysis of 2014 survey of National Influenza Centres in the WHO Global Influenza Surveillance and Response System, 2014e. *Releve epidemiologique hebdomadaire/Section d'hygiene du Secretariat de la Societe des Nations = Weekly Epidemiological Record/Health Section of the Secretariat of the League of Nations.* 89(34) pp. 369–376.

Vanderven, H.A., Ana-Sosa-Batiz, F., Jegaskanda, S., Rockman, S., Laurie, K., Barr, I., Chen, W., Wines, B., Hogarth, P.M., Lambe, T., Gilbert, S.C., Parsons, M.S., Kent, S.J., 2016. What lies beneath: antibody dependent natural killer cell activation by antibodies to internal influenza virus proteins. EBioMedicine 8, 280–293.