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The effect of cross-reactive antibodies on immunogenicity of live-attenuated vaccine: A systems approach

Live-attenuated vaccines (LAV) are reputed to be the most cost-effective tools for controlling epidemics. With increasing disease outbreaks caused by virus infections, vaccines will have to be delivered to both adults and children, who may have pre-existing cross-reactive antibodies due to previous exposure with an antigenically related virus strain. We and others have shown *in vitro* that cross-reactive antibodies can improve vaccine efficacy by enhancing LAV infection in Fc gamma-receptor (FcγR) expressing antigen-presenting cells (APCs), a process known as antibody-dependent enhancement (ADE). However, the relevance and occurrence of ADE has yet to be demonstrated clinically. We conducted an open-label trial where subjects are sequentially immunized with the inactivated Japanese Encephalitis (JE) vaccine (Ixiaro®) followed by a live-attenuated yellow fever (YF) vaccine (Stamaril®). To generate a range of cross-reactive antibodies concentrations, subjects were divided into 3 groups, where they were given JE and YF vaccines at either 1-month (Group 1), 4-months (Group 2) or 9-months (Group 3) apart. Group 4 served as a control where only YF vaccine was administered. A specific range of cross-reactive antibodies from JE vaccination enhanced YF immunogenicity, which is consistent with *in vitro* ADE of virus infection of FcγR-expressing APCs. We further employed a systems biology approach encompassing viremia, transcriptomics, metabolomics and cytokine profiling to explain the molecular basis behind antibody-enhanced YF vaccination. Besides signatures related to increased immunogenicity, we additionally investigated the molecular basis behind reactogenicity. We observed an up-regulation of the innate immune pathways at day 1 post-YF vaccination, and this up-regulation correlated with occurrence of AE. Our findings reveal that the innate immune response can be a double-edge sword, where an early induction results in AE and later induction engenders robust immunity.

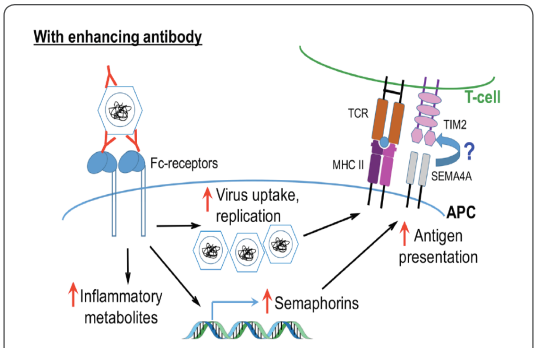

Figure-1: *Collaborating effects of cross-reactive antibodies on YF immunogenicity. YF vaccination triggers up-regulation of interferon-related genes, resulting in antiviral responses that can reduce virus uptake, replication and immunogenicity. However, with enhancing levels of cross-reactive antibodies, YF immune complexes formed can result in increased uptake via antibody-dependent enhancement (ADE) leading to prolonged viremia. In addition, co-ligation of the activating FcγRs by immune complexes under ADE conditions can lead to increased expression of inflammatory metabolites and semaphorins expression that may play crucial roles in antigen-presentation, resulting in eventual improvement in immunogenicity of YF vaccination.*

Recent Publications

1. Gan E S, Cheong W F, Chan K R, Ong E Z, Chai X, Tan H C, Ghosh S, Wenk M R and Ooi E E (2017) Hypoxia enhances antibody-dependent dengue virus infection. *Embo J*; 36(10): 1348-1363.
2. Chan K R, Wang X H, Saron W A A, Gan E S, Tan H C, Mok D Z, Zhang S L, Lee Y H, Liang C, Wijaya L, Ghosh S, Cheung Y B, Tannenbaum S R, Abraham S N, St. John A L, Low J G, Ooi E E (2016) Cross-reactive antibodies enhance live attenuated virus infection for increased immunogenicity. *Nat Microbiol*; 1: 16164.

Biography

Chan Kuan Rong is an Immunologist, specializing in elucidating the role of antibodies in dengue virus infection. He is a Senior Research Fellow in the laboratory of Professor Ooi Eng Eong in the Program of Emerging Infectious Diseases. During his doctoral studies, he identified two co-receptors, Fc-gamma receptor IIB and leukocyte immunoglobulin-like receptor B1, that are involved in antibody-mediated dengue virus neutralization and infection enhancement, respectively. His Postdoctoral research focuses on exploring the use of cross-reactive antibodies to boost efficacy of live vaccines, with the ultimate aim to develop vaccines that are safe and immunogenic.

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