

Immune Response to Yellow Fever Vaccine Examined to a T

March 16, 2015

A Neves

The design of effective vaccines requires a thorough understanding of adaptive immune responses elicited by pathogens of interest. A key component of the adaptive immune system is a type of white blood cell called a T cell. In particular, virus-specific cytotoxic T lymphocytes (CTLs) expand in response to viral infection in order to eliminate infected host cells. A select number of CTLs persist after the infection is resolved and function as memory cells that enable a more efficient immune response to subsequent infections. However, it is not yet clear what distinguishes memory T cells from other T cells that expand after viral infection. The yellow fever vaccine (YFV) yields long-term immunity, and because it uses live attenuated virus, it has become a model to study immune responses to a controlled acute viral infection. A new study published in the *Journal of Virology*, led by Dr. Harlan Robins (Human Biology and Public Health Sciences Divisions), along with Fred Hutch colleagues, analyzed T cell responses to the YFV with unprecedented resolution.

The investigators first administered the YFV to nine healthy volunteers who had not previously received YFV and had no documented prior exposure to the virus. Peripheral blood samples were collected immediately prior to vaccination (day 0), and on days 14 and 90 post-vaccination. Flow cytometry-based cell sorting was used to identify memory T cells present prior to vaccination (day 0), YFV-induced activated effector T cells (TAE in figure; day 14) and both effector and central memory T cells (TEM and TCM in figure; day 90). High-throughput sequencing of the CDR3 region of T cell receptor genes was then used to identify and track YFV-induced T cell clones.

Application of a statistical method developed by the authors revealed that an average of 2000 TAE cell clones were activated by YFV on day 14. To identify which subset remained in the memory compartment, the investigators focused on YFV-induced clones present on day 90, but absent from day 0 samples, and found that 3.1% and 2.5% of clones were recruited to the effector and central memory T cell compartments, respectively. Finally, the authors found that T cell clones that expanded the most in unsorted blood cell samples from day 14 were the most likely to become memory T cells 10 weeks later, and that immunosequencing of unsorted blood samples by itself was sufficient to identify a significant number of YFV-induced clones.

Overall, this study demonstrates the power of combining high-throughput sequencing of the T cell repertoire with statistical analysis to provide an in-depth assessment of the adaptive immune response to vaccines and viral infections, and could be used evaluate the efficacy of novel vaccines. "We identify and track the individual cells of the adaptive immune system that are responding to a pathogen. We learned the scope of the cellular immune response (T cell response) to the yellow fever vaccine and precisely which cells establish long-term memory, " summarized Dr. Robins.

[DeWitt WS, Emerson RO, Lindau P, Vignali M, Snyder TM, Desmarais C, Sanders C, Utsugi H, Warren EH, McElrath J, Makar KW, Wald A, Robins HS.](#) 2015. Dynamics of the Cytotoxic T Cell Response to a Model of Acute Viral Infection. *J Virol.* pii: JVI.03474-14. [Epub ahead of print]

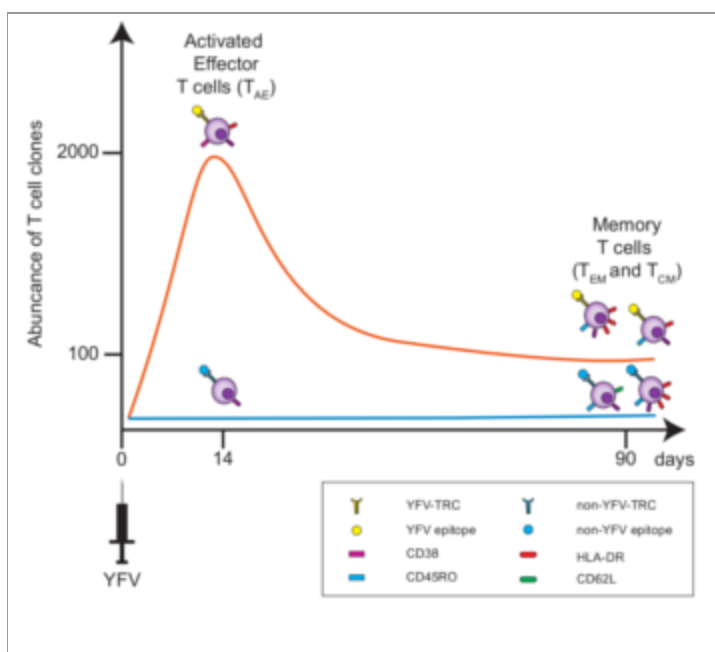


Image provided by Dr. Harlan Robins.

Using a combined flow cytometry, immunosequencing and statistical approach, 2000 activated, effector CD8+ T cell clones (TAE, characterized by the presence of the CD38 and HLA-DR surface markers) were determined to be induced by the yellow fever vaccine (YFV) 2 weeks after vaccination, and approximately 5% of them were identified in the effector (TEM) and central (TCM) memory compartments (CD45RO+ CD62Lhi and CD45RO+ CD62Llo memory CD8+ T cells, respectively) 3 months after vaccination. In addition, the most highly expanded clones were preferentially recruited to the memory compartment, and a fraction of these clones could be identified from peripheral blood solely by measuring clonal expansion. CD8+ T cell clones not induced by YFV are shown for comparison purposes.