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New insights into the mechanism of vaccine-induced T cell immunity

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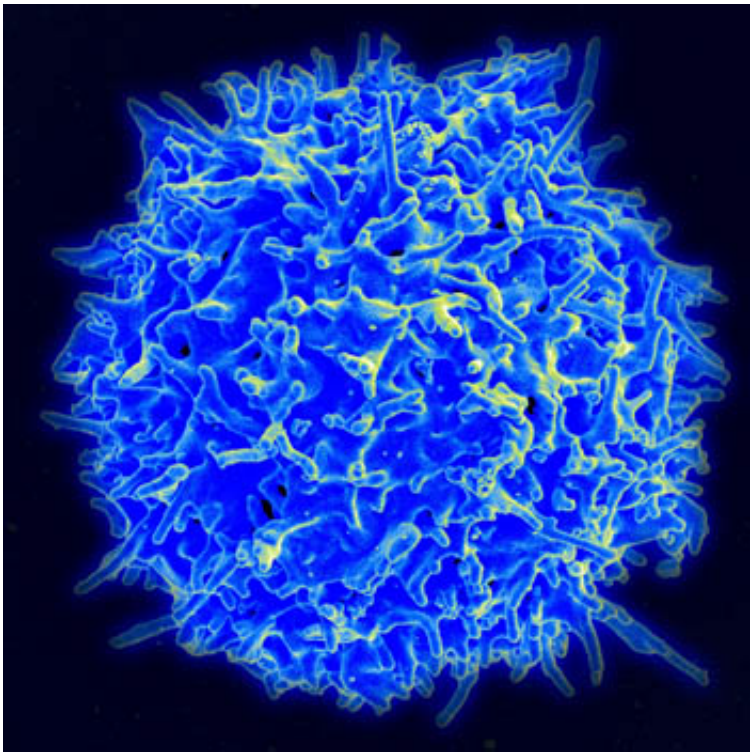

Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

A team led by the Walter Reed Army Institute of Research has gained new insights into the mechanism of vaccine-induced T cell immunity utilizing single-cell RNA sequencing and metabolic profiling techniques. Though numerous vaccines induce and amplify T cells, a critical part of the body's adaptive immune system, there is still an information gap

regarding what determines the magnitude, diversity and persistence of that response.

This study, published in *Nature Communications*, was conducted at the WRAIR Viral Diseases Branch in partnership with the Department of Cell and Molecular Biology, Institute for Immunology and Informatics at the University of Rhode Island. It utilized samples from a Phase 1 clinical trial for TAK-003, a live-attenuated tetravalent dengue vaccine.

Dengue virus, present in four distinct serotypes, infects up to 280-500 million individuals yearly around the world. Though many recover quickly from dengue infection, approximately 500,000 develop severe dengue disease, a condition with an approximately 2.5% mortality rate. Dengue is of particular concern for deploying Service Members, and the development of effective countermeasures to prevent dengue infection is a priority for the Department of Defense.

In cases where a patient experiences dengue infection from one serotype and is then re-infected with a distinct dengue serotype, the likelihood of developing severe disease increases significantly. This complicates development of a dengue vaccine, which needs to induce a protective response against all four serotypes and ensure that severe dengue is not induced as a result of the vaccine. A robust T cell response is considered a vital part of immunity to dengue and other viral diseases.

The TAK-003 vaccine, developed to protect against all four serotypes, has been shown to be safe and immunogenic in small animal models and non-human primates. In this study, techniques such as single-cell transcriptomic analysis, or the analysis of the RNA present within a cell, combined with more standard means of cellular immune monitoring shed significant light into the regulation, gene expression and metabolic pathways of T cells. Particularly notable was the discovery of a marker, transferrin receptor 1 (TfR1), to identify the differentiation potential of

CD8+ cells, suggesting that T cell immunity is dependent on the availability of specific metabolites.

"The DoD Dengue Vaccine Program strives to understand mechanisms to enhance protection from diseases and to maximize the physical potential of the soldier. This collaborative effort with a partner's vaccine suggests that targeting the unique metabolic requirements of the immune cells thought to provide protection from dengue infection may contribute in the establishment of protective immunity following vaccination," said Lt. Col. Richard Jarman, an author on the paper and director of the Viral Diseases Branch. Though these discoveries took place in the context of a dengue vaccine trial, they are applicable to the development of vaccines for numerous viral diseases.

More information: Adam T. Waickman et al, Dissecting the heterogeneity of DENV vaccine-elicited cellular immunity using single-cell RNA sequencing and metabolic profiling, *Nature Communications* (2019). DOI: 10.1038/s41467-019-11634-7

Provided by Walter Reed Army Institute of Research