Memory B cell marker predicts long-lived antibody response to flu vaccine

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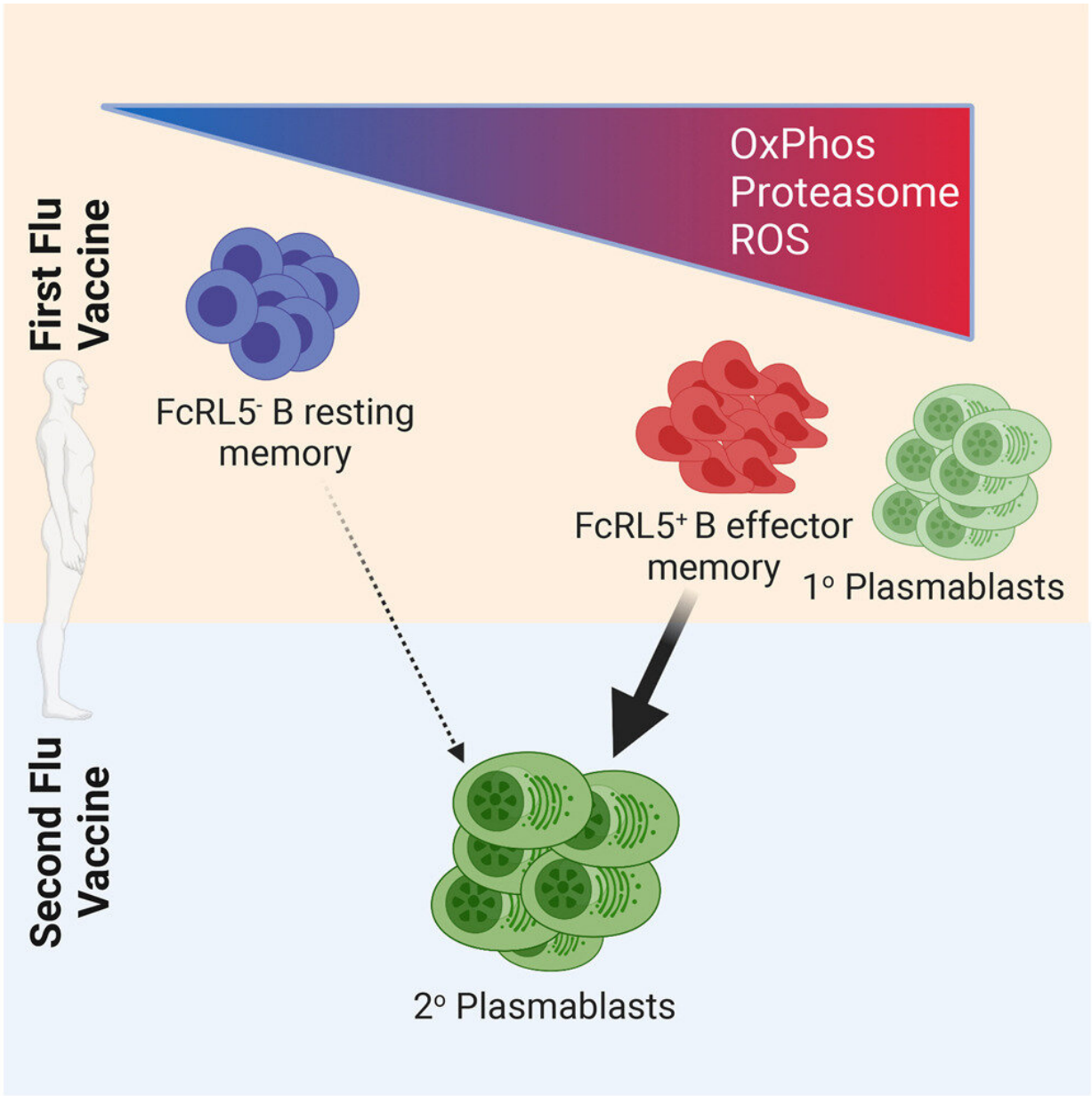

Credit: *Immunity* (2023). DOI: 10.1016/j.immuni.2023.03.001

Memory B cells play a critical role to provide long-term immunity after a vaccination or infection. In a study published in the journal *Immunity*, researchers describe a distinct and novel subset of memory B cells that predict long-lived antibody responses to influenza vaccination in humans.

These effector memory B cells appear to be poised for a rapid serum antibody response upon secondary challenge one year later, Anoma Nellore, M.D., Fran Lund, Ph.D., and colleagues at the University of Alabama at Birmingham and Emory University report. Evidence from transcriptional and epigenetic profiling shows that the cells in this subset differ from all previously described memory B cell subsets.

The UAB researchers identified the novel subset by the presence of FcRL5 receptor protein on the cell surface. In immunology, a profusion of different cell surface markers is used to identify and separate immune cell types. In the novel memory B cell subset, FcRL5 acts as a surrogate marker for positive expression of the T-bet transcription factor inside the cells. Various transcription factors act as master regulators to orchestrate the expression of many different gene sets as various cell types grow and differentiate.

Nellore, Lund and colleagues found that the $FcRL5^{+}$ $T\text{-}bet^{+}$ memory B cells can be detected seven days after immunization, and the presence of these cells correlates with vaccine antibody responses months later. Thus, these cells may represent an early, easily monitored cellular compartment that can predict the development of a long-lived antibody response to vaccines.

This could be a boon to the development of a more effective yearly influenza vaccine. "New annual influenza vaccines must be tested, and then manufactured, months in advance of the winter flu season," Lund said. "This means we must make an educated guess as to which flu strain will be circulating the next winter."

Why are vaccine candidates made so far in advance? Pharmaceutical companies, Lund says, need to wait many weeks after vaccinating volunteers to learn whether the new vaccine elicits a durable immune response that will last for months. "One potential outcome of the current study is we may have identified a new way to predict influenza vaccine durability that would give us an answer in days, rather than weeks or months," Lund said. "If so, this type of early 'biomarker' could be used to test flu vaccines closer to flu season—and moving that timeline might give us a better shot at predicting the right flu strain for the new annual vaccine."

Seasonal flu kills 290,000 to 650,000 people each year, according to World Health Organization estimates. The global flu vaccine market was more than $5 billion in 2020.

To understand the *Immunity* study, it is useful to remember what happens when a vaccinated person subsequently encounters a flu virus.

Following exposure to previously encountered antigens, such as the hemagglutinin on inactivated influenza in flu vaccines, the immune system launches a recall response dominated by pre-existing memory B cells that can either produce new daughter cells or cells that can rapidly proliferate and differentiate into short-lived plasmablasts that produce antibodies to decrease morbidity and mortality. These latter B cells are called "effector" memory B cells.

"The best vaccines induce the formation of long-lived plasma cells and

memory B cells," said Lund, the Charles H. McCauley Professor in the UAB Department of Microbiology and director of the Immunology Institute. "Plasma cells live in your bone marrow and make protective antibodies that can be found in your blood, while memory B cells live for many years in your lymph nodes and in tissues like your lungs.

"Although plasma cells can survive for decades after vaccines like the measles vaccine, other plasma cells wane much more quickly after vaccination, as is seen with COVID-19," Lund said. "If that happens, memory B cells become very important because these long-lived cells can rapidly respond to infection and can quickly begin making antibody."

In the study, the UAB researchers looked at B cells isolated from blood of human volunteers who received flu vaccines over a span of three years, as well as B cells from tonsil tissue obtained after tonsillectomies.

They compared naïve B cells, FcRL5^{+} T-bet^{+} hemagglutinin-specific memory B cells, FcRL5^{neg} T-bet^{neg} hemagglutinin-specific memory B cells and antibody secreting B cells, using standard phenotype profiling and single-cell RNA sequencing. They found that the FcRL5^{+} T-bet^{+} hemagglutinin-specific memory B cells were transcriptionally similar to effector-like memory cells, while the FcRL5^{neg} T-bet^{neg} hemagglutinin-specific memory B cells exhibited stem-like central memory properties.

Antibody-secreting B cells need to produce a lot of energy to churn out antibody production, and they also must turn on processes that protect the cells from some of the detrimental side effects of that intense metabolism, including controlling the dangerous reactive oxygen species and boosting the unfolded protein response.

The FcRL5^{+} T-bet^{+} hemagglutinin-specific memory B cells did not express the plasma cell commitment factor, but did express

transcriptional, epigenetic and metabolic functional programs that poised these cells for antibody production. These included upregulated genes for energy-intensive metabolic processes and cellular stress responses.

Accordingly, FcRL5^{+} T-bet^{+} hemagglutinin-specific memory B cells at Day 7 post-vaccination expressed intracellular immunoglobulin, a sign of early transition to antibody-secreting cells. Furthermore, human tonsil-derived FcRL5^{+} T-bet^{+} memory B differentiated more rapidly into antibody-secreting cells in vitro than did FcRL5^{neg} T-bet^{neg} hemagglutinin-specific memory B cells.

Lund and Nellore, an associate professor in the UAB Department of Medicine Division of Infectious Diseases, are co-corresponding authors of the study, "A transcriptionally distinct subset of influenza-specific effector memory B cells predicts long-lived antibody responses to vaccination in humans."

More information: Anoma Nellore et al, A transcriptionally distinct subset of influenza-specific effector memory B cells predicts long-lived antibody responses to vaccination in humans, *Immunity* (2023). DOI: 10.1016/j.immuni.2023.03.001

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