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How antiviral antibodies become part of immune memory

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Weapons production first, research later. During wartime, governments follow these priorities, and so does the immune system.

When fighting a bacterial or viral infection, an otherwise healthy person will make lots of antibodies, blood-borne proteins that grab onto the invaders. The immune system also channels some of its resources into research: storing some antibody-making cells as insurance for a future encounter, and tinkering with the antibodies to improve them.

In humans, scientists know a lot about the cells involved in immediate antibody production, called plasmablasts, but less about the separate group of cells responsible for the "storage/research for the future" functions, called memory B cells. Understanding how to elicit memory B cells, along with plasmablasts, is critical for designing effective vaccines.

Researchers at Emory Vaccine Center and Stanford's Department of Pathology have been examining the precursors of memory B cells, called activated B cells, after influenza vaccination and infection and during Ebola virus infection. The Ebola-infected patients were the four who were treated at Emory University Hospital's Serious Communicable Disease Unit in 2014.

The findings are scheduled for publication in *Nature Immunology*.

"Ebola virus infection represents a situation when the patients' bodies were encountering something they've never seen before," says lead

author Ali Ellebedy, PhD, senior research scientist at Emory Vaccine Center. "In contrast, during both influenza vaccination and infection, the immune system generally is relying on recall."

Unlike plasmablasts, activated B cells do not secrete antibodies spontaneously, but can do so if stimulated. Each B cell carries different rearrangements in its DNA, corresponding to the specificity and type of antibody it produces. The rearrangements allowed Ellebedy and his colleagues to track the activated B cells, like DNA bar codes, as an immune response progresses.

Ellebedy and Rafi Ahmed, PhD, director of Emory Vaccine Center, teamed up with Katherine Jackson, PhD and Scott Boyd, PhD at Stanford to analyze the DNA bar codes. All work with Ebola specimens was performed at the Centers for Disease Control and Prevention's biosafety level 4 facility. Collaborators from St. Jude Children's Research Hospital contributed to the paper.

A week after flu immunization, both flu-specific plasmablasts and flu-specific activated B cells could be detected in volunteers' blood. Two weeks after immunization, the plasmablasts had disappeared, but the activated B cells were still proliferating, the researchers report. Similarly, as Ebola infection progressed, more activated B cells were observed in patients' blood while the proportion of plasmablasts declined.

"This difference in timing following infection or vaccination may reflect a preference for the immune system to first rapidly generate plasmablasts whose antibodies directly engage the foreign antigens," the authors write.

Analyzing the antibody DNA bar codes showed that the codes overlapped between the plasmablasts and activated B cells, indicating

that they came from common ancestors. However, most sequences were found only in one group of cells. The authors show that a couple months after flu immunization, many of the activated B cells had settled down and had become resting memory B cells.

The authors highlight an intriguing finding, which was that the level of antibody tinkering - known as somatic hypermutation - did not increase in volunteers' B cells over time after seasonal flu immunization.

While this result may suggest that seasonal flu immunization has diminishing returns, Ellebedy says that it is partly because study participants were all adults who had probably been exposed to flu viruses before. Thus, their flu-specific B cells may have already been optimized in previous encounters. The B cells analyzed in this study were those specific for the 2009 H1 flu protein, a part of the seasonal flu vaccine that has not changed in recent years (volunteers were vaccinated between 2012 and 2015).

"It is still worthwhile to encourage the immune system to make a greater quantity of antibodies, even if their quality does not rise appreciably, and the value of vaccination may be greater when the flu vaccine strains are not identical to those used in previous seasons' vaccines," he says.

More information: Defining antigen-specific plasmablast and memory B cell subsets in human blood after viral infection or vaccination, *Nature Immunology*, DOI: 10.1038/ni.3533

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