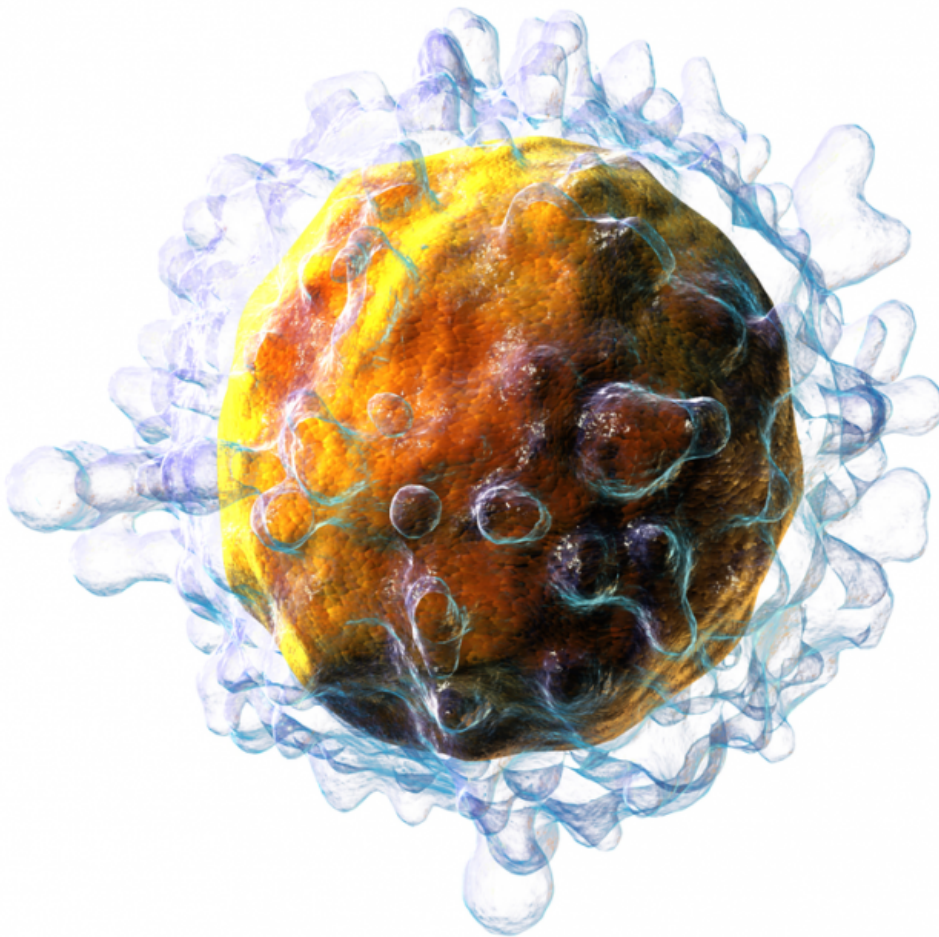


Researchers discover how cells remember infections decades later

December 14 2017



3D rendering of a T cell. Credit: CC BY 3.0, Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762.

A perplexing question in immunology has been, how do immune cells remember an infection or a vaccination so that they can spring into action decades later? Research led by scientists at the University of California, Berkeley, in collaboration with investigators at Emory University, has found an answer: A small pool of the same immune cells that responded to the original invasion remain alive for years, developing unique features that keep them primed and waiting for the same microbe to re-invade the body.

Before this study, scientists were not sure how cells can remember an infection from up to 30 years earlier. To tease apart this mystery, the research team tracked a specific kind of immune cell through the human body in the weeks, months and years following a vaccination that gives long-term protection.

The researchers tracked T cells inside people's bodies after they were given the long-lasting yellow fever virus vaccine, using a technology developed at Berkeley for monitoring the birth and death of cells in humans over long periods of time. The researchers found that CD8+ T cells, responsible for long-term immunity against yellow fever, proliferate rapidly on exposure to the vaccine but then evolve, beginning about four weeks after the vaccination, into a "memory pool" of cells that live more than 10 times longer than the average T cell.

"This work addressed fundamental questions about the origin and longevity of human memory CD8+ T cells generated after an acute infection," said Marc Hellerstein, senior coauthor and professor of nutritional science and toxicology at UC Berkeley. "Understanding the basis of effective long-term immune memory may help scientists develop better vaccines, understand differences among diseases and diagnose the quality of an individual person's immune responses."

The study will be published December 13 in the journal *Nature*. The

work was supported by grants from the National Institutes of Health.

When someone gets a vaccine or is exposed to a new infectious agent, cells that recognize the invader but had never have been called into action before - called naive cells - respond by dividing like crazy and developing infection-fighting functions. This creates a large pool of so-called memory cells, named for their ability to remember the specific infectious agent and respond effectively to repeat threats later. Over time, the large pool shrinks to a small number of long-term memory cells, which are primed to provide late protection. But scientists have debated how these memory cells are maintained and ready to strike for so long after the initial exposure.

This study found that one way the pool is maintained for years after vaccination is through the development of several unique features. On the surface and through the actions of their genes, they look like cells that have never been exposed to an infection, but on their DNA the researchers found a fingerprint, called a methylation pattern, that identifies them as having been through battle as an infection-fighting cell, which are called [effector cells](#).

"These cells are like veteran soldiers, camped in the blood and tissues where they fight their battles, waiting for yellow fever to show up," said Hellerstein. "They are resting quietly and they wear the clothes of untested new recruits, but they are deeply experienced, ready to spring into action and primed to expand wildly and attack aggressively if invaders return."

For the study, Hellerstein applied a technique that he developed for his HIV/AIDS research in the 1990s and has used widely since to track the birth and death of cells in the human body. The research team had subjects drink small amounts of water that had deuterium instead of hydrogen. Deuterium is non-toxic, but it is slightly heavier than

hydrogen, so scientists can track it by mass spectrometry when it gets incorporated into newly replicated DNA in the body's cells, which occurs only during cell division. Using this method, scientists can learn if a pool of cells is new or old, because newly born cells will have deuterium in their DNA. Scientists or clinicians monitoring the cells over time will see that the deuterium levels in short-lived cells will be diluted after the patients return to drinking regular water, while the deuterium levels in long-lived cells will remain high. In the new study, people drank the deuterium water at different times after receiving the live yellow fever virus vaccine and researchers isolated T cells from the patients, then analyzed their deuterium content.

Yellow fever virus is not a threat in the United States, which means that all the subjects had not been previously exposed and would not get exposed after the tagging period, making the vaccine ideal for studying what happens to newly generated cells over a long period of time, when there is no longer any infectious agent to fight.

After a first acute exposure to an infectious agent or vaccine, the body has an initial phase with lots of short-lived infection fighting soldiers, called effector-memory cells. Then after the threat is cleared, effector cells go away and small numbers of long-term memory cells are present. One of the central questions in immunology was whether the long-term memory cells went through an effector stage or went on a separate pathway of their own. The research team found that that a subset of the effector-memory pool that had divided extensively during the first two weeks after vaccination stayed alive as long-term memory cells, dividing less frequently than once every year.

The extremely long life-span of the surviving memory cells allows them to specialize over time into a unique, previously unrecognized type of T cell. The long-term memory cells have some molecular markers that make them look like naive cells that have never activated, including a

gene expression profile that looks like that in naive cells, yet have other molecular markers on their DNA of having gone through battle as effector cells.

"These results make it clear that true long-term memory cells were once effector cells that have become quiescent," Hellerstein said. "This apparently keeps them poised to respond rapidly as new effector cells upon re-exposure to the pathogen."

The research team calculated that the half-life of these long-term memory cells is 450 days, compared to a half-life of about 30 days for the average memory T cell in the body, during which they are in general repeatedly exposed to common antigens in the environment. So when the [memory](#) pool goes quiet, these unique cells retain a fingerprint stemming back to the original exposure, and remain primed to respond rapidly if there is re-exposure to the pathogen.

"The combination of molecular evidence of a unique life history with direct measurement of their long life span is what gives this study such power," Hellerstein said. "The technology to measure the dynamics of the birth and death of cells and advances allowing it to be applied to very small numbers of [cells](#) let this study happen."

More information: Rama S. Akondy et al. Origin and differentiation of human memory CD8 T cells after vaccination, *Nature* (2017). [DOI: 10.1038/nature24633](https://doi.org/10.1038/nature24633)

Provided by University of California - Berkeley

Citation: Researchers discover how cells remember infections decades later (2017, December 14) retrieved 9 April 2024 from <https://phys.org/news/2017-12-cells-infections-decades.html>

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