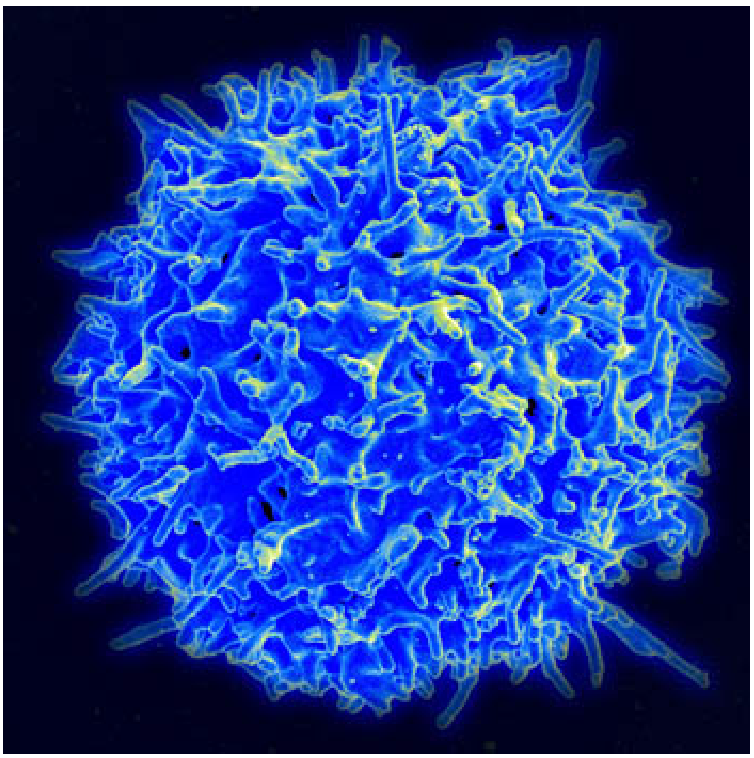
Medical Xpress

Video imaging reveals how immune cells sense danger

May 11 2017



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

How do T cells, the beat cops of the immune system, detect signs of disease without the benefit of eyes? Like most cells, they explore their surroundings through direct physical contact, but how T cells feel out intruders rapidly and reliably enough to nip infections and other threats in the bud has remained a mystery to researchers.

In a new study, published online May 11, 2017 in *Science*, UC San Francisco researchers began to address this question by using cutting-edge techniques to capture videos of the surface of living T cells in more detail than ever before. Researchers had previously observed tentacle-like protrusions called microvilli covering the surface of T cells, but the new research revealed that these tentacles are in constant motion: they crawl across the cell surface, each independently searching for signs of danger or infection in a fractal-like pattern that allows T cells to spend the minimum time necessary feeling for a potential threat before moving on.

"Previous techniques had allowed us to take snapshots of the surface of T cells, but that's like trying to understand a basketball game by studying a black-and-white photo," said Matthew Krummel, PhD, associate professor of pathology at UCSF and senior author of the new study. "Now we can watch these amazing little fingers of membrane move around in real-time - and it turns out they're incredibly efficient."

Among other potential benefits, Krummel says, understanding how T cells efficiently sample their environment to search for invasive pathogens opens up new questions about what countermeasures infectious organisms or even cancer cells may have evolved as a way of avoiding detection, and could suggest new ways for researchers to help T cells see through such a ruse.

Efficient search by T cells is key to an effective immune response

As they make their rounds through the body, T cells make contact with a network of informants—other immune cells that scour the body for potential signs of danger and display the protein fragments they find (called "antigens") on their surface for inspection by the T cells. If a T cell meets one of these so-called antigen-presenting cells and recognizes a protein fragment it carries as evidence of danger, the T cell sounds the alarm and triggers a more global immune response to fight off the invaders.

Scientists estimate that you have only about 100 T cells in your body at any given moment that can recognize and responding to a specific antigen, such a protein from this year's flu virus, and these few cells each take days to patrol your entire body, Krummel said. "This means the immune system really needs to get ahead of whatever is attacking the body at the very first evidence that there's an intruder on board. If one T cell misses the signs of a virus, the next time a cell that can recognize the threat might come through that tissue, the virus has had hours to make tens of thousands of copies of itself."

New imaging techniques reveal how immune cells "talk" using touch

In the *Science* study, Krummel's team was able to study how T cells efficiently interrogate antigen-presenting cells in real time, thanks to a high-resolution cellular imaging technique called lattice light-sheet microscopy, which the team set up at UCSF in collaboration with its inventor, 2014 Nobel prize winner and study co-author Eric Betzig, PhD, of the Howard Hughes Medical Institute's Janelia Research Campus in Virginia.

Using this technology, the team studied mouse T cells exploring simulated patches of antigen-presenting cell membrane in laboratory dishes, and found that the T cell microvilli move independently of one another in a fractal-like geometry, such as is often seen in nature as a way of optimizing efficient use of space, such as by plant roots or foraging animals.

The researchers calculated that, thanks to this efficient search pattern, in an average minute-long encounter win an antigen-presenting cell, T cell microvilli can thoroughly explore 98 percent of the contact surface between the two cells—called an "immunological synapse" after the neuronal synapses of the nervous system. This suggests that T cells are tuned to spend the minimum time necessary to get a clear read on the information available at each antigen-presenting cell before moving on, the authors say.

To study the details of threat detection by microvilli, the authors devised a new approach that allowed them to simultaneously track microvilli as well as the T cell receptor (TCR) proteins T cells use to detect their target antigens. To do this, the team covered simulated patches of antigen-presenting cell membrane with tiny fluorescent particles called quantum dots, which questing T cell microvilli had to push out of the way to reach the membrane surface. This technique, dubbed synaptic contact mapping, allowed the researchers to visualize the microvilli as holes of negative space in the quantum dot fluorescence, while at the same time visualizing TCRs with a different-colored fluorescent marker.

They found that normally, individual microvilli poke and prod at the antigen-presenting cell membrane for an average of about four seconds at a time. But when the microvilli found the antigen they were searching for, they stayed in contact with the antigen-presenting cell membrane for 20 seconds or more and accumulated large rafts of TCRs, suggesting that they were likely signaling the T cell to trigger its immune response.

"These videos give me a much more visceral understanding of what's happening when T cells and antigen-presenting cells come into contact," Krummel said. "T cells have these anemone-like sensory organs, and when they want to get information from another cell, their only chance appears to be during this short period of intimate contact. If they don't detect a strong signal during that contact, they move on."

Real-time imaging technology opens new opportunities to study immunity and disease

Krummel's team also briefly studied the surfaces of other types of immune cells, such as dendritic cells and B cells, which play different roles in pathogen detection and immune response. They found that each cell type appears to use distinct patterns of surface protrusions—such as tentacles, waves, or curtain-like ripples—to probe and communicate with their environments, though more research is needed to understand these diverse patterns and how they interact with one another. (See video.)

"Understanding how the immune system reliably detects and responds to the huge range of potential threats it has to deal with is one of the key questions we still face as immunologists," Krummel said. "Of course, the immune system also makes mistakes—like when it attacks the body's own cells in autoimmune disease or fails to recognize cancerous cells as a threat. Understanding the mechanics and constraints of how the immune system recognizes threats in the first place could potentially help us correct those errors."

More information: "Visualizing dynamic microvillar search and stabilization during ligand detection by T cells" *Science* (2017). science.sciencemag.org/cgi/doi … 1126/science.aal3118

Provided by University of California, San Francisco