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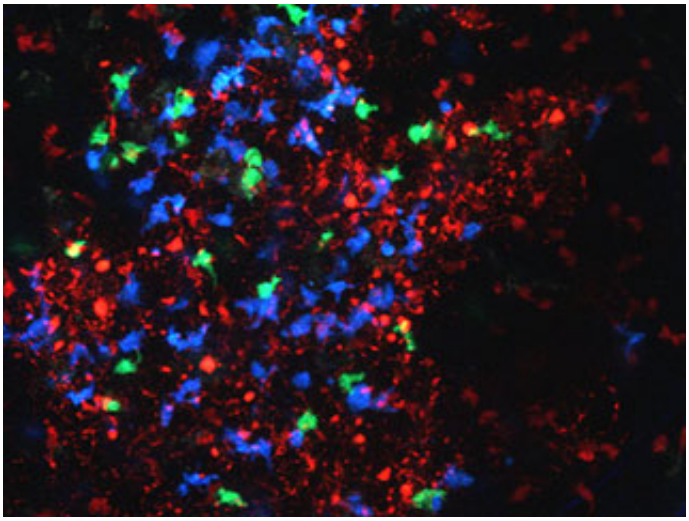
Cell division speeds up as part of antibody selection, study shows

July 16 2015



The immune system produces antibodies finely tuned to target a foreign protein, called an antigen. Recent research describes how the interaction between T cells (green) and B cells (blue) allows this to take place. Bystander B cells and antigen appear in red. Credit: Laboratory of Molecular Immunology at The Rockefeller University

It's a basic principle of immunology: When a germ invades, the body adapts to that particular target and destroys it. But much remains unknown about how the immune system refines its defensive proteins, called antibodies, to most effectively zero in on that invader. Experiments at The Rockefeller University offer new insight into the details of this selection process.

In research published in *Science* on July 16, scientists led by Michel Nussenzweig, Zanvil A. Cohn and Ralph M. Steinman Professor and head of the Laboratory of Molecular Immunology, uncovered a new mechanism by which the B cells that produce the most finely tuned antibodies rise to dominance. This discovery builds on earlier work published last year.

"Through a process called affinity maturation B cells compete, and those cells that produce the highest affinity antibodies win and come to dominate the B cell population. Our work so far has revealed two of the mechanisms that allow high affinity B cells to overwhelm the others," says Alex Gitlin, a graduate student in the lab and first author of the paper.

B cells have genes that code for antibodies, which latch onto foreign proteins, called antigens, as part of an immune response. During an infection, B cells and other immune cells form tiny structures called germinal centers in the spleen and lymph nodes.

Within germinal centers, B cells evolve in a Darwinian-like fashion. The gene responsible for producing their antibodies mutates rapidly, a million times faster than the normal rate of mutation in the human body, and the cells proliferate. B cells whose mutations increase the antibody's affinity for the antigen are selected, and these cells then continue to mutate and proliferate.

"Previously, we showed that high affinity cells spend more time dividing and mutating in between rounds of competition. We now show that these high affinity cells also use this additional time more effectively—by dividing at faster rates," Gitlin says. In this manner, the germinal center produces the high affinity antibodies that are the basis of an effective immune response.

Vaccines initiate this process by exposing the body to pieces of a pathogen or to a weakened or dead version of it, prompting the immune system to develop protective antibodies. Because vaccines depend on effective antibody responses for protection, a better understanding of the antibody selection process in the germinal center might potentially be of use for developing more effective vaccines.

The team's research has focused on the dynamics inside the germinal center. Within it, B cells travel between two areas known as the dark zone and the light zone. In the dark zone, the B cells mutate and proliferate, before traveling to the light zone, where they pick up pieces of antigen. The higher the affinity of their antibodies, the more antigen they pick up.

Their previous experiments demonstrated that another type of immune cell, the T cell, operates in the light zone to recognize the higher affinity B cells based on the amount of antigen they display. The more antigen the B cells present to T cells, the stronger the signal the T cells send. As a result, the high affinity B cells spend more time in the dark zone in between visits to the light zone.

This time, the team, which also included collaborators at Memorial Sloan Kettering Cancer Center and Harvard Medical School, identified another reason the high affinity cells come to dominate: more rapid cell divisions. They induced the selection of an engineered set of B cells in mice, and used labels that the cells incorporate as they replicate their DNA in preparation for cell division. With these techniques they found that a signal from the T cell also prompts the high affinity B cells to divide more rapidly while in the dark zone. In effect, these cells have both more time and more speed with which to duplicate themselves.

By labeling DNA replication and following its progression, the team took a close look at how the S phase of the cell cycle, in which the cell

copies its DNA in preparation for division, is sped up. They found that acceleration during this phase was due to the double-stranded DNA molecule being unzipped and copied more rapidly at the so-called replication fork.

"Together, these studies describe two complementary ways in which signals from T cells empower the best equipped set of B cells to take over the immune response during affinity maturation. Other mechanisms, which are yet to be discovered, are also likely to be at play," Gitlin says. "The dynamics of germinal centers are crucial to this basic immunological process, and they may also have important implications for improving vaccines and understanding lymphomas, which often arise from germinal center B cells due to their high rates of proliferation and mutation."

Nussenzweig is also a senior physician at The Rockefeller University Hospital and a Howard Hughes Medical Institute investigator.

More information: "T cell help controls the speed of the cell cycle in germinal center B cells": www.sciencemag.org/lookup/doi/ … 1126/science.aac4919

Provided by Rockefeller University

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