How two different types of immune cells help two billion people keep tuberculosis in check

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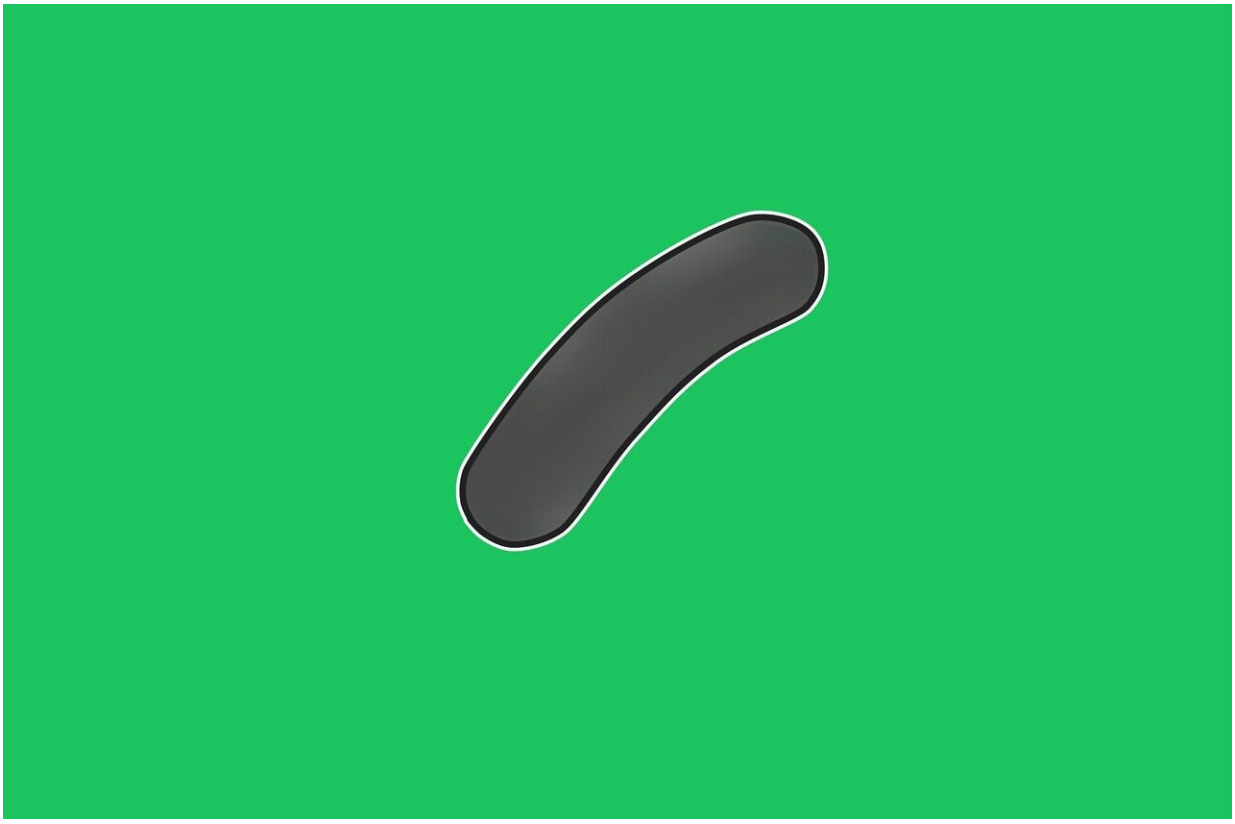

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More than 10 million people are sickened by tuberculosis (TB) globally each year, resulting in 1.5 million deaths. Yet, as many as two billion people are infected with Mycobaterium tuberculosis, the bacterium that

causes tuberculosis, and are otherwise healthy and asymptomatic. Scientists who study TB look at those individuals who can tolerate and contain the infection in hopes of developing better treatments and vaccines.

The key feature of tuberculosis infection in humans is the formation of granulomas, or clusters of immune cells in the lungs that contain the infection. These granulomas contain B cells, all-purpose immune cells that perform a variety of functions, from producing antibodies to regulating the activity of other cells. For years, researchers assumed that these B cells must be performing a specific direct function in the granulomas to control TB infection, but in a new study, scientists from the University of Chicago and Washington University in St. Louis show that these B cells are actually directing reinforcements to help.

In the study, published in *Nature Immunology*, the team eliminated different expected B cell functions one by one in animal models of TB to narrow down the possibilities for which components prevented progression of disease. Nothing seemed to make a difference, whether removing plasma cells that produce antibodies or knocking out other B cell functions that produce immune signaling molecules.

"No matter what we knocked out individually in B cells, it didn't make a difference. All the predicted functions that people think B cells are doing were not what they were doing in the lung for protection against TB," said Shabaana Khader, Ph.D., the Bernard and Betty Roizman Professor and Chair of Microbiology at UChicago and senior author of the study. "But they needed to be there, because when we knocked TB-specific B cells out completely, you start seeing that the mice get sick. So, we knew that it wasn't any of these usual suspects."

In addition to the results in mice, the team saw the same results when they completely deleted B cells in non-human primate models.

B cells aren't the only immune cells present in granuloma tissue. T cells, another important white blood cell of the immune system, also play a part, specifically CD4+ or "helper" T cells that can initiate immune responses. Both B and T cells interact to control tuberculosis progression, but until this study, just how much either contributed and interacted wasn't completely clear.

As Khader and her team narrowed down the potential functions of the B cells, they saw that the helper T cells express transcription factors that in turn generate T cell subtypes, including T follicular helper (Tfh)-like cells that localize within the granuloma tissue. It is these Tfh-like cells that activate macrophages to keep the TB infection in check by surrounding and killing infected cells, but the B cells tell them where to go and localize within the granulomas. So, instead of directly controlling TB themselves, B cells are pointing the Tfh-like cells in the right direction to do the job.

"An effective way to activate macrophages is to get Tfh-like cells to come there and activate them, and that's what the B cell is doing," Khader said.

The only vaccine for tuberculosis was first produced in 1921, and while it's effective in preventing some forms of childhood TB, its protection is widely variable for adults. Understanding how some people are able to control TB infection naturally could help develop better versions in the future.

"If you can initiate the protective immune response much earlier, the bacteria will never get a chance to establish infection in the lung," Khader said. "We could make a vaccine that generates the right kind of immune response so that when you get exposed to the bacteria, you won't even carry the latent infection. So, our resolution for vaccine design is much cleaner now since we know what cell types to target in

the lung."

The study is titled "Antigen-specific B cells direct T follicular- like helper cells into lymphoid follicles to mediate Mycobacterium tuberculosis control."

More information: Deepak Kaushal, Antigen-specific B cells direct T follicular-like helper cells into lymphoid follicles to mediate Mycobacterium tuberculosis control, *Nature Immunology* (2023). DOI: 10.1038/s41590-023-01476-3.
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