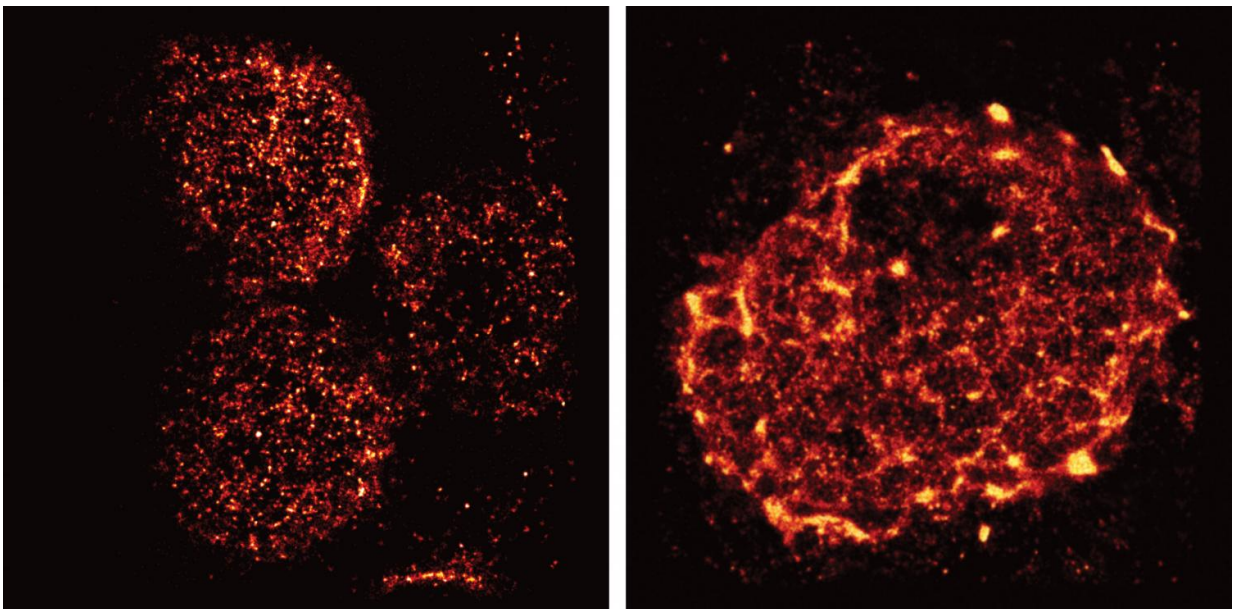


Super-resolution microscopy reveals unprecedented detail of immune cells' surface

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Salk scientists used light-sheet super-resolution imaging to capture the rearrangement of T-cell receptors from nanometer-scale protein islands (left) to micrometer-scale microclusters (right) after T-cell activation in mouse lymph nodes. Credit: Salk Institute

When the body is fighting an invading pathogen, white blood cells—including T cells—must respond. Now, Salk Institute researchers have imaged how vital receptors on the surface of T cells bundle

together when activated.

This study, the first to visualize this process in lymph nodes, could help scientists better understand how to turn up or down the immune system's activity to treat autoimmune diseases, infections or even cancer. The results were published this week in the *Proceedings of the National Academy of Sciences*.

"We had seen these [receptors](#) cluster and reposition in [cultured cells](#) that were artificially stimulated in the lab, but we've never seen their natural arrangements in lymph nodes until now," says senior author Björn Lillemeier, an associate professor in Salk's Nomis Laboratories for Immunobiology and Microbial Pathogenesis, and the Waitt Advanced Biophotonics Center.

T cells are activated when receptors embedded in their outer membrane bind to other [immune cells](#) that have digested an antigen, such as a virus, bacteria or cancer cell. In turn, the activated T cells switch on cellular pathways that help the body both actively seek out and destroy the antigen and remember it for the future. In the past, by looking at T-[cell receptors](#) embedded in isolated cells under the microscope, researchers discovered that the receptors are arranged in clusters—called protein islands—that merge when the cells are activated.

Lillemeier wanted more detail on how the receptors are arranged in tissue and how that arrangement might change when the T cells are activated in living hosts. The team used a super-resolution microscope developed in the laboratory of co-senior author Hu Cang, assistant professor at Salk's Waitt Advanced Biophotonics Center and holder of the Frederick B. Rentschler Developmental Chair. This microscopy approach, called light-sheet direct stochastic optical reconstruction microscopy (dSTORM), let the researchers watch T cell receptors in the membranes of T cells in mouse [lymph nodes](#) at a resolution of

approximately 50 nanometers.

The new imagery confirmed the previous observation that protein islands of T-cell receptors merge into larger "microclusters" when T cells are activated. But it also showed that, before cells are activated, the protein islands are already arranged in groups—dubbed "territories" by Lillemeier's team. "The pre-organization on the molecular level basically turns the T cell into a loaded gun," says Lillemeier.

The organization of [surface receptors](#) enables T cells to launch fast and effective immune response against antigens. Understanding how the molecular organization mediates the sensitivity of T cell responses could help researchers make the immune system more or less sensitive. In the case of autoimmune diseases, clinicians would like to turn down the immune system's activity, while turning up the activity could help fight infections or cancers.

The research could also have implications for understanding other receptors in the body, which have a wide range of functions both within and outside the immune system. "We think that most receptors on the surfaces of [cells](#) are organized like this," says Ying Hu, first author and postdoctoral researcher at the Salk Institute.

More information: Ying S. Hu et al, Superresolution imaging reveals nanometer- and micrometer-scale spatial distributions of T-cell receptors in lymph nodes, *Proceedings of the National Academy of Sciences* (2016). [DOI: 10.1073/pnas.1512331113](https://doi.org/10.1073/pnas.1512331113)

Provided by Salk Institute

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