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LJI scientists discover how T cells transform to defend our organs

Future drugs could target specialized T cells to help the body fight tumors, infections, and more

LA JOLLA, CA—We owe a lot to tissue resident memory T cells (T_{RM}). These specialized immune cells are among the body's first responders to disease.

Rather than coursing through the bloodstream—as many T cells do—our T_{RM} cells specialize in defending specific organs. They battle viruses, breast cancer, liver cancer, melanomas, and many other health threats.

Pandurangan Vijayanand, M.D., Ph.D., William K. Bowes Distinguished Professor at La Jolla Institute for Immunology (LJI), has even shown that a greater density of T_{RM} cells is linked to better survival outcomes in lung cancer patients.

Now Vijayanand and his colleagues have discovered the cellular driver that leads to T_{RM} cell development. Their findings, published recently in *Science Immunology*, offer a potential way to boost T_{RM} cell numbers to better fight disease.

“We found a new molecule that is likely to play an important role in the development and function of T_{RM} cells," says Vijayanand.

Scientists reveal a hidden cell signal

There are many kinds of T cells, and they play different parts in defending the body. Some T cells kill infected cells, others alert their neighbors to danger. Memory T cells, such as T_{RM} cells, learn to recognize invaders and patrol the body to make sure past threats don't take over.

T_{RM} cells are special because they live in just one organ environment. For a long time, these special cells flew under the radar. T_{RM} cells were only formally described as a distinct memory T cell population in 2009.

Thanks to advances in immune cell profiling, researchers at LJI are uncovering how these cells work and how we might harness them to improve human health. "This is a super powerful cell population," says Han Feng, Ph.D., Postdoctoral Fellow in the Vijayanand Lab at LJI and co-first author of the new study.

So how does a T cell become a T_{RM} cell?

It all comes down to cell signaling. Like all immune cells, T_{RM} cells have a cell membrane that is covered with special receptor molecules. Immune cells need these receptors to bring in signals from their surroundings. Some molecular signals tell immune cells when it is time to transform and specialize to do a certain job in the body. This process of transformation is called cell differentiation.

In a previous study, Vijayanand and his colleagues found that T_{RM} cells are studded with a membrane receptor molecule called G-protein coupled receptor 25 (GPR25). This high level of GPR25 expression is unusual. "That was so specific, so we knew there must be something going on with this receptor," says Feng.

In their new study, the LJI scientists are the first to show that GPR25 is induced by a signaling molecule called TGF-β. GPR25 sustains TGF-β downstream signaling, which promotes a process called differentiation, during which a regular memory T cell transforms into a T_{RM} cell.

To learn more about this process, Feng spearheaded experiments to study T_{RM} cells in a genetically engineered mouse model. She focused on the mouse lung tissue and liver tissue, where T_{RM} cells are critical for fighting infections and tumors.

Feng's work confirmed the importance of GPR25. She found that mice with GPR25 deficiency don't sustain TGF-β signaling properly and cannot maintain a functional population of T_{RM} cells. Further experiments suggested that tweaking GPR25 activity could work as a way to enhance or suppress T_{RM} cells activity.

Next steps for drug development

Future therapeutics might target GPR25 to help the body fight disease. In fact, that process of drug development may be relatively straightforward.

G protein-coupled receptor (GPCR) molecules, such as GPR25, are exceptionally "druggable," explains Feng. The structure of these receptor molecules makes them fairly easy to target, compared with other drug targets. Plus, the receptors are helpfully exposed on the cell surface. "These molecules are expressed on the cell membrane, so they are easy for a drug to access," Feng says.

Many medications—from heart disease drugs to diabetes therapeutics—already take advantage of GPCR molecules. Around 30 percent of drugs approved by the U.S. Food and Drug Administration target this G protein-coupled receptor "superfamily."

Feng says future therapeutics might target GPR25 to enhance T_{RM} cell populations in infectious diseases and cancers. It may also be possible to modulate GPR25 activity to suppress T_{RM} cell functions and treat autoimmune diseases where T_{RM} cells contribute to harmful inflammation.

"We think GPR25 is an interesting molecule full of translation potentials that worth investigating," says Feng.

Additional authors of the study, "GPR25 promotes the formation of lung and liver tissue-resident memory CD8 T cells," are Sungjun Park (co-first author), Jae Woo Shin, Francisco Emmanuel Castañeda Castro, Job Rocha Hernandez, Benjamin J. Schmiedel, Changlu Liu, Michael R. Jackson, and Christian H. Ottensmeier.

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