Medical Xpress

Enhancing immune defenses: Researchers unveil the secrets of specialized T cells to conquer tumors

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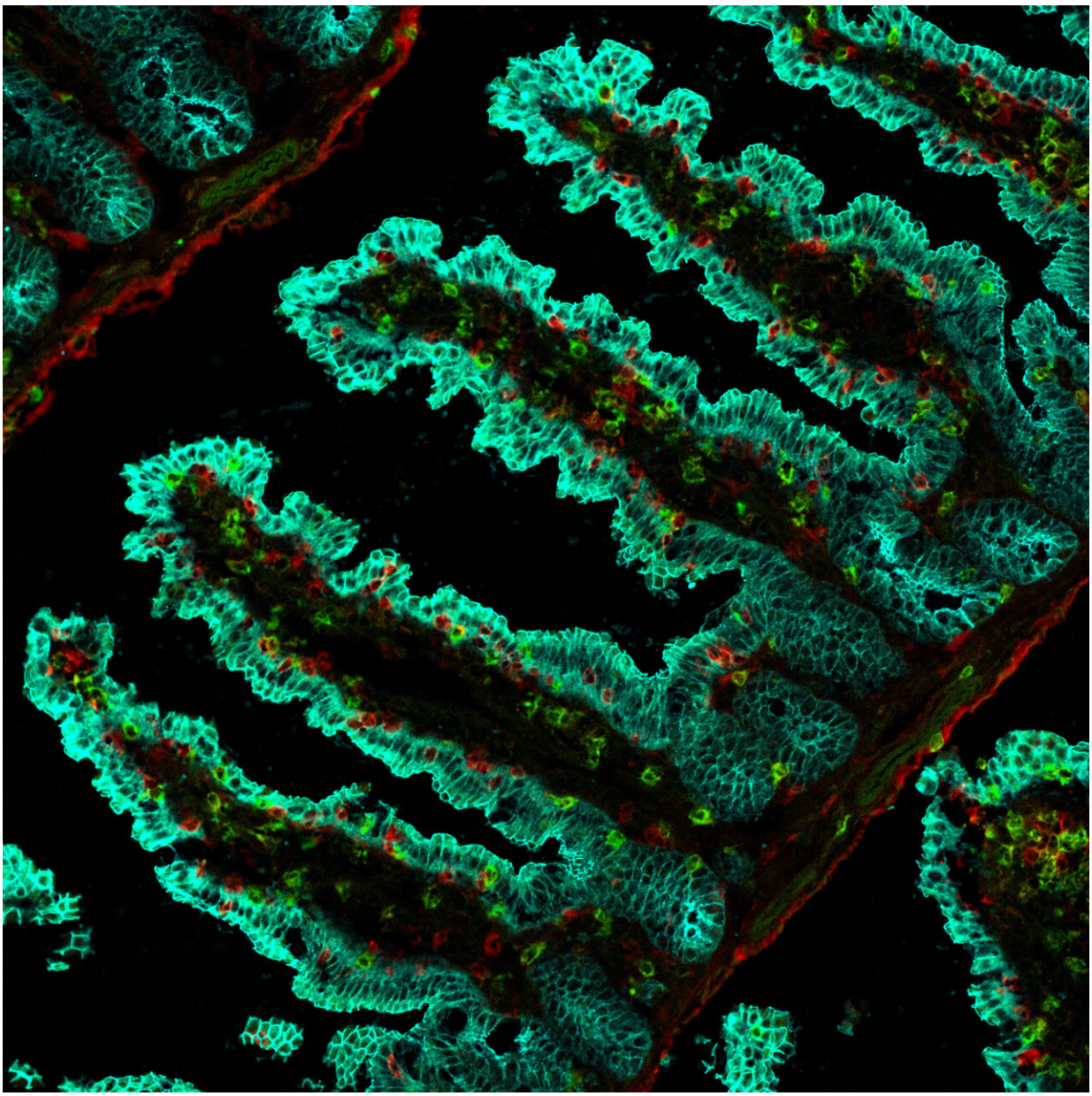


Researchers captured microscopic photographs of specialized cells of the immune system known as tissue-resident CD8 T cells (epithelial cells are shown in cyan, immune cells in a combination of green and red), seen here in the small intestine. Credit: Kianoosh Mempel

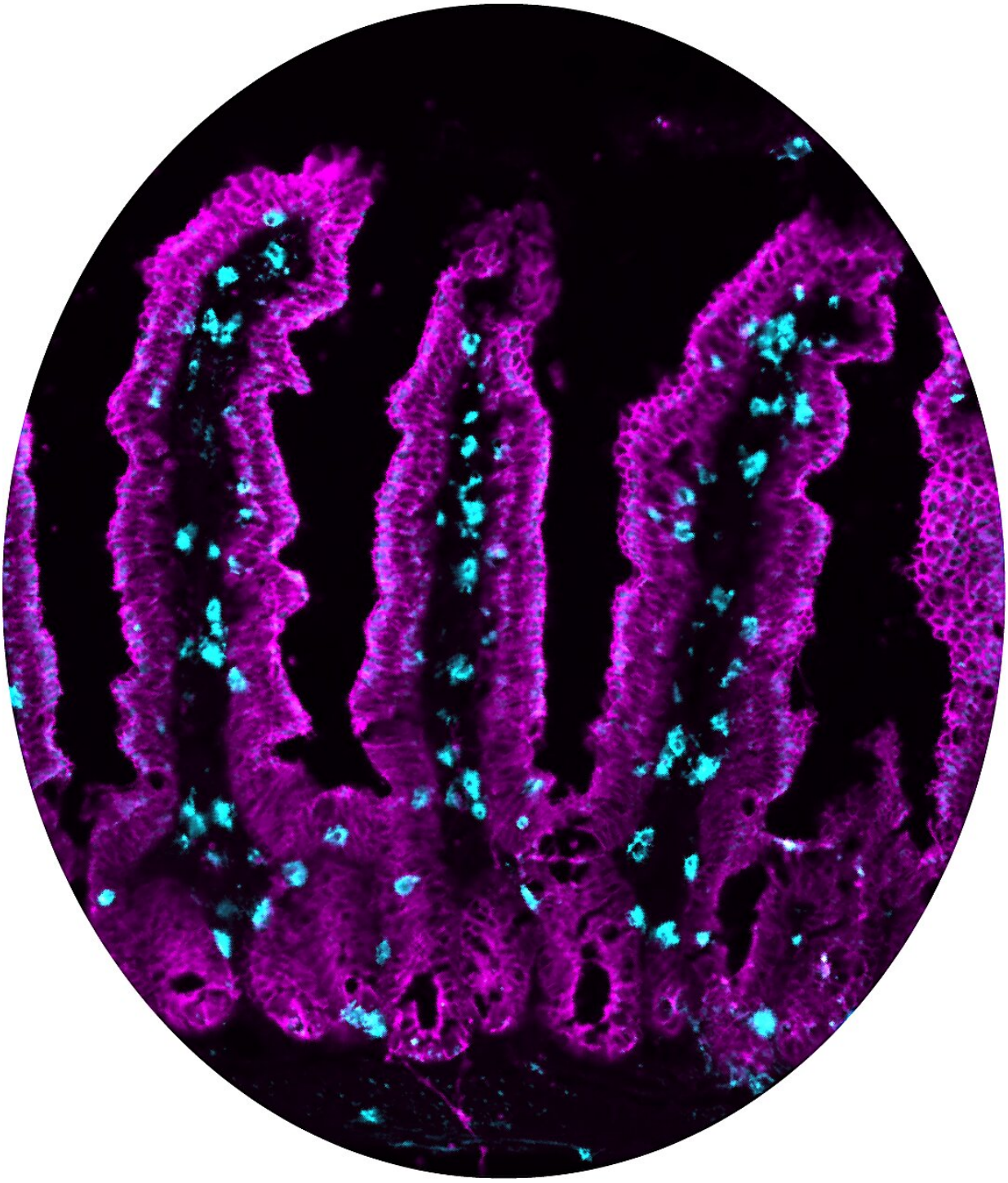
Our immune system has an ingenious trick up its sleeve. It remembers past foes, stopping potential sickness in its tracks through a phenomenon known as immunological memory. This is thanks to specialized cells—tissue-resident memory T cells—which reside in vital organs like the small intestine, lungs and other areas. Consider them as frontline guards, stationed exactly where trouble could strike. The endurance of these cells is extraordinary, protecting us from infections we fought decades ago.

Investigations led by University of California San Diego Postdoctoral Scholar Miguel Reina-Campos, Professor Ananda Goldrath and their collaborators at the University of California San Diego and several other institutions have revealed new insights into the metabolism of these specialized immune cells and how they could be enhanced as immune defense weapons against infections and tumors.

"T cells destined for a life-long deployment at barrier tissue sites are professional survivalists," said Goldrath, a professor in the School of Biological Sciences' Department of Molecular Biology and senior author of the new paper. "These cells are extremely good at safeguarding tissues across the body, and understanding their unique adaptation strategies teaches us how to design better immune therapeutics."

The scientific team set out to determine whether these powerful T cells

could be tapped for immune system defense and learn more about how such processes unfold. Their findings are published in the journal *Nature* and include co-authors from the David Geffen School of Medicine at UCLA, UC San Francisco, La Jolla Institute for Immunology, UC San Diego School of Medicine, St. Jude Children's Research Hospital in Memphis, Tenn. and the University of North Carolina.



Immunologists used microscopy images of the small intestines of mice to study specialized immune cells (epithelial cells colored magenta and tissue-resident memory CD8 T cells in cyan). Credit: Kianoosh Mempel

"The immune system excels at coping with pathogens and infections, but it struggles against tumors," said Reina-Campos, the study's first author. The researchers wondered if these remarkable cells hold the key to unlocking a new era of immune system innovation. This is especially relevant in the battle against stubborn tumors. Picture your immune cells adapting, thriving and evolving within their organ strongholds.

The researchers delved deep, investigating the function of thousands of genes fueling these cells' survival strategy. They ultimately found that T cells in tissue showed a large increase in the complicated production machinery that makes cholesterol molecules. However, a surprising puzzle emerged as the cells appeared primed to make cholesterol, yet a cholesterol-rich diet dampened their effectiveness.

It turns out, these clever cells also produce an energy-boosting molecule, coenzyme Q, needed to power the cell's batteries (mitochondria), as they journey through the intricate process of creating cholesterol.

"What most surprised me is how sensitive and responsive these cells are to the diet," said Reina-Campos, who noted that cells feature built-in sensor systems that play into their decision-making.

"Nature likes cost-effective solutions. If a T cell senses an overabundance of cholesterol, it will shut off the entire internal production line that makes it, the same way you would probably stop grocery shopping and cooking if somebody were to provide free cooked meals daily." These cells are resourceful and will take what they have available to them, but that is not always in their best interest, he said.

Armed with this new knowledge, the team devised an ingenious way to redirect the cells' cholesterol-making prowess towards producing more coenzyme Q. Think of it as rerouting a river to nourish different landscapes.

Benefiting the research was the existence of a drug that was harnessed to orchestrate this transformative redirection, supercharging the immune cells for a more successful life in tissues.

"We are very excited because we found an existing drug that puts this blockade exactly where we need it. When we apply these disruption technologies in the context of tumors, we help T cells maintain fully charged batteries so they can better fight off tumors in mice," said Reina-Campos.

Another powerful approach to modulating this pathway included statin drugs, which millions use to inhibit the formation of cholesterol and treat cardiovascular disease. The authors found that statins halted the charging of T cell's batteries; thus, fewer memory cells were found in the tissues. This was because statins block the pathway too far upstream, stopping the production of key molecules for the mitochondria.

Although the beneficial cardiovascular effect of statins is undisputable, these results prompt further studies to understand these immunomodulatory effects. On the flip side, statins could offer new insights and tools to dampen unwanted T cell activation in tissues.

More information: Ananda Goldrath, Metabolic programs of T cell tissue residency empower tumour immunity, *Nature* (2023). DOI: 10.1038/s41586-023-06483-w.
www.nature.com/articles/s41586-023-06483-w

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