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Text by Ben Short
bshort@rockefeller.edu

Lymphocytes shrink to stay fit

Researchers describe how immune cells quickly adapt to cytokine withdrawal and nutrient stress.

In response to an infection, proinflammatory cytokines stimulate lymphocytes to take up nutrients so that they can proliferate and mount an immune response. Once the infection is cleared, however, cytokine levels decline and the lymphocytes' nutrient supply is abruptly cut off. Most of the cells quickly die by apoptosis, but a small fraction survive and differentiate into long-lived memory cells that can be reactivated if infection occurs again. Hecht et al. reveal that these cells adapt to their reduced nutrient intake by quickly changing their volume and density (1).

Memory cells survive the nutrient stress that follows cytokine withdrawal by several different mechanisms. They express anti-apoptotic proteins such as Bcl-2 (2), they switch to more efficient metabolic pathways (3), and, crucially, they activate autophagy to degrade and recycle their cytoplasmic content (4). But a team of researchers led by Matthew Vander Heiden and Scott Manalis at the Koch Institute at the Massachusetts Institute of Technology discovered that lymphocytes also undergo an acute biophysical response to cytokine withdrawal that could help them adapt to nutrient deprivation (1).

Using a suspended microchannel resonator, the researchers measured the volume and density of apoptosis-resistant pro–B cells after removing the stimulatory cytokine IL-3, and found that the lymphocytes dramatically shrank—and increased their density—in the first 24 hours after cytokine withdrawal. The reduction in cell volume was mainly driven by a loss of cytoplasmic content. "The cells become more dense, so one of the biggest things they must be losing is water," explains Vander Heiden. "But they also lose a large amount of RNA and a little bit of protein and lipid."

This initial loss of cytoplasmic content isn't driven by autophagy, however. The most dramatic changes in cell volume occurred before the autophagy pathway was switched on, and still took place if autophagy was inhibited. The researchers—including first authors Vivian Hecht and Lucas Sullivan—therefore wondered whether the volume and density changes might represent an earlier adaptation to nutrient stress.

Hecht et al. confirmed that the apoptosis-resistant pro–B cells decreased their nutrient and oxygen consumption upon IL-3 withdrawal, indicating that their capacity for ATP production was greatly reduced. "Yet the cells are still alive and their ATP levels are not significantly altered," Vander Heiden says. "So they must be decreasing their ATP consumption."

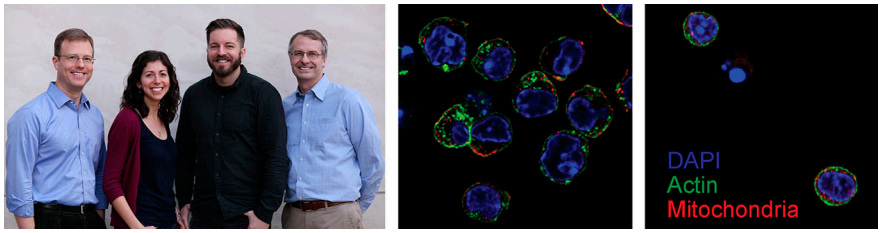
> "This shrinking behavior… allows the cells to decrease their ATP consumption."

Cells expend a large amount of energy maintaining the integrity and electrical potential of their plasma membranes. "We realized that this shrinking behavior allows the cells to decrease their ATP consumption," Vander Heiden explains. "It greatly reduces the cells' surface area and therefore saves a lot of energy, giving the cells time to activate the autophagy program."

This early biophysical adaptation could therefore be crucial for memory cell differentiation. Indeed, Hecht et al. found that primary $CD8^+$ T cells underwent similar volume and density changes when the pro-inflammatory cytokine IL-2 was replaced with the differentiation-promoting factor IL-15. Moreover, the researchers speculate that, by preferentially retaining proteins and other dense components of the cytoplasm, the cells contain plenty of material that can be recycled by the autophagy pathway while the memory cells remain dormant, or even reused if the cells are reactivated to fight a new infection.

The next step, explains Vander Heiden, is to investigate the molecular and cell biological mechanisms underlying the changes in cell volume and density. How do the lymphocytes preferentially rid themselves of certain components? "Cells are in water, so how they eliminate water over other things is a really interesting question," Vander Heiden says.

FOCAL POINT



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A team of researchers including (left to right) Scott Manalis, Vivian Hecht, Lucas Sullivan, and Matthew Vander Heiden investigate the initial response of lymphocytes to the withdrawal of proinflammatory cytokines and the consequent reduction in nutrient uptake. The researchers find that pro–B cells (center) dramatically shrink and increase their density in the first 24 hours after IL-3 withdrawal (right). This biophysical adaptation reduces the cells' surface area, and therefore decreases the amount of energy required to maintain the integrity and electrical potential of their plasma membranes. The response may help lymphocytes survive and differentiate into memory cells that can be reactivated to fight subsequent infections.

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