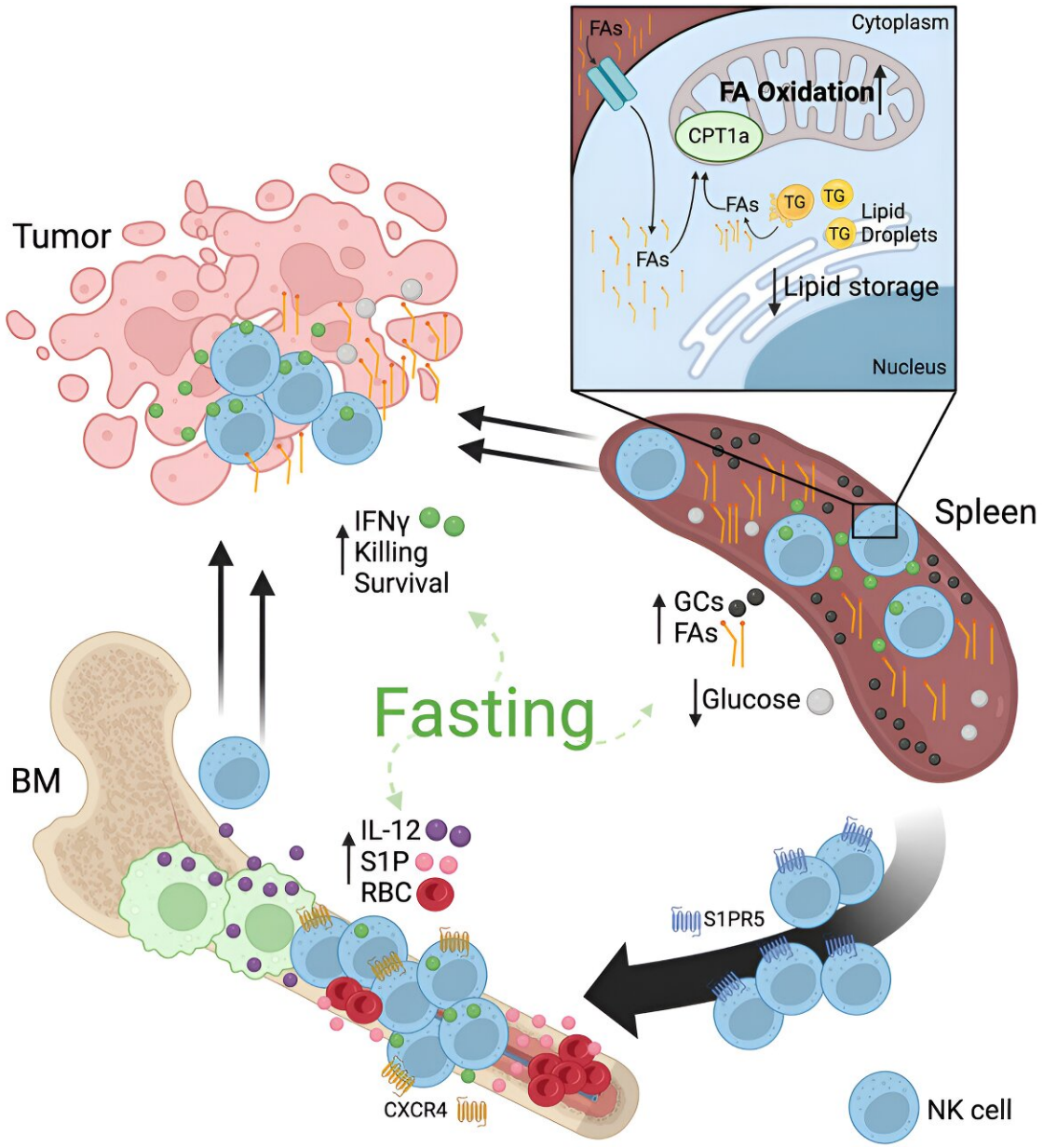
Medical Xpress

Fasting primes the immune system's natural killer cells to better fight cancer, new study in mice finds

June 14 2024, by Ian Demsky



Graphical abstract. Credit: *Immunity* (2024). DOI: 10.1016/j.immuni.2024.05.021

Periods of fasting reprogram the immune system's natural killer cells to better fight cancer, according to a new study in mice from researchers at Memorial Sloan Kettering Cancer Center (MSK).

Fasting and other dietary regimens are increasingly being explored as ways to starve cancer cells of the nutrients they need to grow and to make cancer treatments more effective.

Now a team of researchers from MSK's Sloan Kettering Institute and their collaborators have shown for the first time that fasting can reprogram the metabolism of natural killer cells, helping them to survive in the harsh environment in and around tumors, while also improving their cancer-fighting ability. The study, led by postdoctoral fellow Rebecca Delconte, Ph.D., was published June 14 in *Immunity*.

The findings could help explain one of the mechanisms by which fasting may help the body defend against cancer—along with more generally reducing fat and improving metabolism. And while more research is needed, the results also suggest fasting could be a strategy to improve immune responses to make immunotherapy more effective, the study authors note.

"Tumors are very hungry," says immunologist Joseph Sun, Ph.D., the study's senior author. "They take up essential nutrients, creating a hostile environment often rich in lipids that are detrimental to most immune cells. What we show here is that fasting reprograms these natural killer

cells to better survive in this suppressive environment."

What are natural killer cells?

Natural killer cells, or NK cells for short, are a type of white blood cell that can kill abnormal or damaged cells, like cancer cells or cells infected with a virus. They get their name because they can destroy a threat without ever having encountered it before—unlike T cells, which require prior exposure to a specific enemy to mount a targeted response.

In general, the more NK cells that are present within a tumor, the better the prognosis is for the patient.

For the study, mice with cancer were denied food for 24 hours twice a week, and then allowed to eat freely in between fasts. This approach prevented the mice from losing weight overall, the authors note.

But these periods of fasting had a profound effect on NK cells.

Just as happens in humans, the mice saw a drop in their glucose levels and a rise in free fatty acids, which are lipids released by fat cells that can serve as an alternative energy source when other nutrients aren't present, Dr. Delconte says.

"During each of these fasting cycles, NK cells learned to use these fatty acids as an alternative fuel source to glucose," she says. "This really optimizes their anti-cancer response because the tumor microenvironment contains a high concentration of lipids, and now they're able enter the tumor and survive better because of this metabolic training."

Fasting reprograms NK Cells

The fasting also led to a redistribution of NK cells within the body, the researchers observed.

Many of the NK cells traveled into the bone marrow, where, thanks to the fasting, they were exposed to high levels of a key signaling protein called Interleukin-12. This primed the NK cells to produce more Interferon-gamma—a cytokine that plays an important role in anti-tumor responses.

Meanwhile, NK cells in the spleen were undergoing a separate reprogramming, making them better at using lipids as a fuel source.

"With both of these mechanisms put together, we find that NK cells are pre-primed to produce more cytokines within the tumor," Dr. Delconte says. "And with the metabolic reprogramming, they're more able to survive in the tumor environment, and specialized to have improved anti-cancer properties."

It's unclear yet whether there are two separate populations of NK cells that get trained differently in different parts of the body, or whether the cells end up passing through both sites during their weeks-long life cycle.

"That's the million-dollar question," Dr. Sun says. "And one that we have only begun to answer using the cell-labeling techniques we used in this study."

While human bone marrow samples weren't studied as part of the project, the researchers note that blood samples from cancer patients show that fasting causes a reduction of freely circulating NK cells in people, just as they observed in mice.

Potential to improve cancer treatments

There are several potential opportunities to advance the mouse-model research toward the clinic, the researchers say. First, clinical trials are already beginning to study the safety and effectiveness of fasting in combination with standard existing treatments.

Another avenue would be to identify drugs that could target the underlying mechanisms without requiring patients to fast. Third, NK cells might be able to be put into a fasted state outside of the body, and then be administered to improve treatment effects.

At present, however, more clinical data is still needed about the effects of fasting for people with cancer, says Neil Iyengar, MD, an MSK breast medical oncologist and leading researcher on diet, metabolism, and cancer, who was not directly involved in the study.

"There are many different types of fasting, and some might be helpful while others might be harmful," he says. "Patients should speak with their doctors about what's safe and healthy for their individual situation."

More information: Rebecca B. Delconte et al, Fasting reshapes tissue-specific niches to improve NK cell-mediated anti-tumor immunity, *Immunity* (2024). DOI: 10.1016/j.immuni.2024.05.021

Provided by Memorial Sloan Kettering Cancer Center