IN THE LAB

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Like a vampire, some cancer cells can suck the energy source from immune cells

By Angus Chen Oct. 13, 2023

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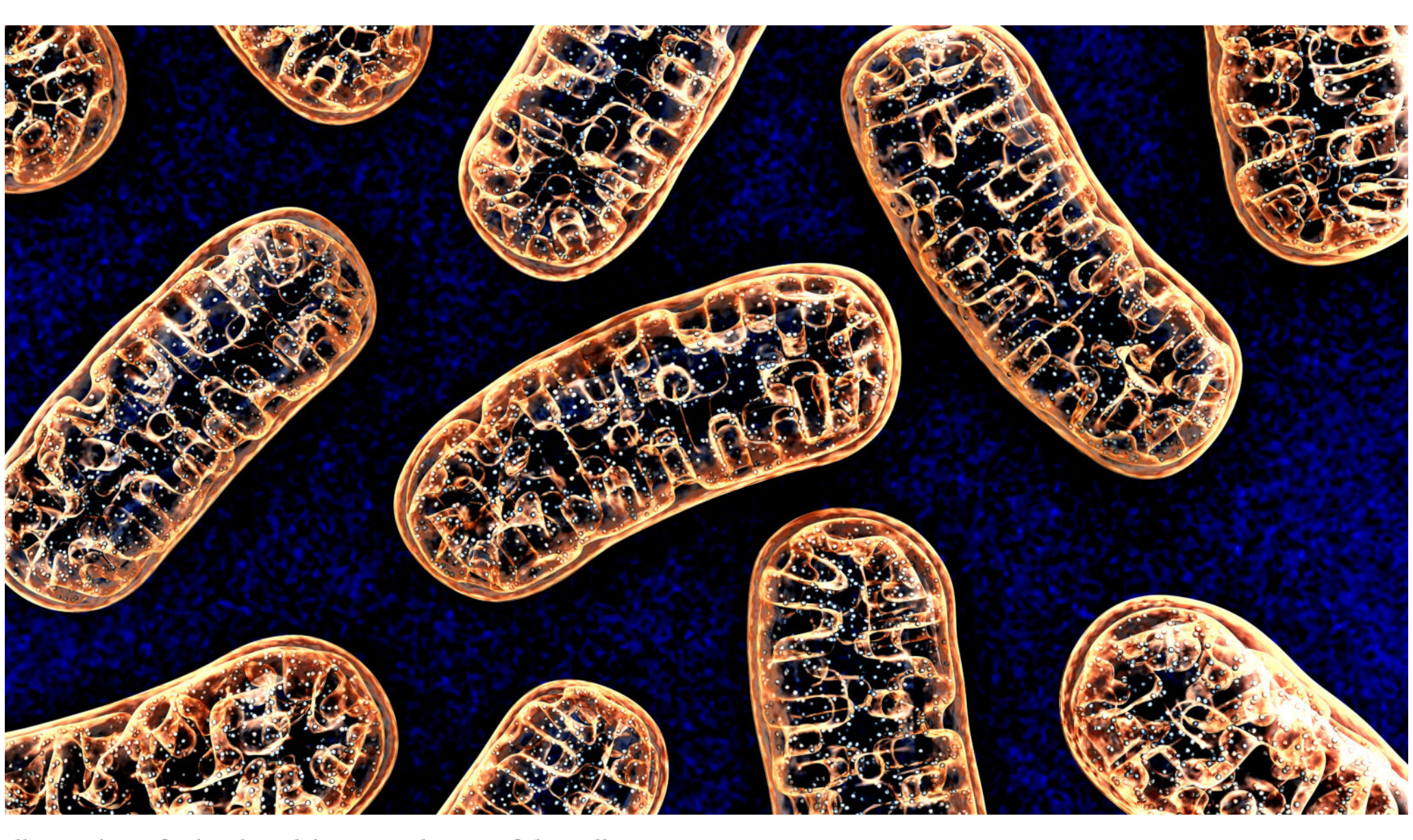

Illustration of mitochondria, powerhouse of the cell.
ADOBE

As elite hunters of the immune system, T cells are constantly prowling our bodies for diseased cells to attack. But when they encounter a tumor, something unexpected can happen. New research shows that some cancer cells can fire a long nanotube projection into the T cell that, like a vampire's fang, sucks energy-creating mitochondria from the immune cell, turning the predator into prey.

A study published this week in Cancer Cell investigated how cancer cells can rob mitochondria from T cells, shutting the immune cell down while energizing themselves. It may be yet another way cancer overcomes both the body's defenses and resists many immunotherapies like CAR-T therapy and immune checkpoint blockade drugs, experts said.

"This is a new mechanism of immune evasion. It seems like the cancer cells are draining mitochondria from the T cells," said Bo Li, a cancer researcher at the University of Pennsylvania and a senior author on the paper. "It's really amazing. Some of my colleagues, their reaction was like, 'I can't believe this is true.' I understand that. It's just like the cancer cell is too smart."

Mitochondria, sometimes called the powerhouse of the cell, generate all the energy that cells need to operate. They most likely arose when an ancient cell engulfed some proto-organism, which eventually evolved into the modern organelle. That's probably why mitochondria have a separate genome, a double membrane, and possibly some proclivity toward moving around. Cells can share mitochondria, Li said, and will occasionally exchange them between each other.

"In some settings, mitochondria can be transferred to repair damaged cells," he said. "Mitochondria can also be damaged. Horizontal transfer is a way to keep the mitochondrial homeostasis so cells will stay healthy. But transfer between cancer cells and T cells is a very new finding."

One clear observation of this phenomenon in cancer came in a Nature Nanotechnology 2021 paper. A team led by Brigham and Women's Hospital cancer researcher Shiladitya Sengupta used a scanning electron microscope to photograph cancer cells extending long tendrils that encircled and trapped nearby T cells, almost like the tail of a hungry python. Within them, mitochondria can be seen draining from the T cell and into the cancer cell.

"It's a stunning picture. You kind of have to see it to believe it. Cancer cells are actually doing this," Sengupta said. "But it's a pretty significant phenotype. It's not like rare. A lot of groups have seen it. People sent me pictures after we published saying, 'we saw this before but we didn't know it was important.'"

The new study provides greater clarity on how crucial this mechanism is for patients and cancer outcomes, said Sengupta, who did not work on the study. "A big question was, yeah, mitochondria get transferred. So what? This paper shows that if this happens, those patients have a poorer outcome. That's an advancement over what we had seen," he said. "They went on to say this happens because the cancer cells doing this have a certain genetic signature. It gives us a starting point to start looking at how and why the mitochondria are getting hijacked."

To do the study, UPenn's Li ran a couple of key experiments. In one, the team cultured T cells and cancer cells in the lab and stained their mitochondria green and red, respectively. Then, when the cells were mixed, the scientists could watch as the green-stained mitochondria from the T cells gradually migrated into the cancer cells, but not the other way around. "The cancer cell becomes stained green, meaning the T cell's mitochondria are flowing into the cancer cell. The T cells are either still green or they lose their signal," Li said. "They become dark."

A micrograph shows cancer cells extending tentacles into ball-like T cells.
COURTESY NATURE NANOTECHNOLOGY

In follow-up experiments, the researchers sequenced the transcriptomes, the array of genes that were actively turned on, in the robber cancer cells and compared them to cancer cells that weren't actively robbing mitochondria. That helped them construct a genetic signature that indicates if a cancer cell is likely to engage in mitochondrial theft. When the team looked for that genetic signature in the Cancer Genome Atlas, a large patient tumor database, they found it correlated with worse survival as well as some signs that the cancer was more rapidly proliferating.

In theory, cancer's ability to feed on immune cells might also help explain why some immunotherapies have had limited efficacy against solid tumors, experts said, since many of these therapies use engineered T cells or invoke T cells to attack cancer.

"Any T cell entering a tumor microenvironment, this is where things get dicey," said Greg Delgoffe, an immunologist at the University of Pittsburgh and Hillman Cancer Center who didn't work on the study. "Whether that's a CAR-T cell or endogenous T cells already there, their mitochondria are stolen straight from them. I find that idea to be extremely exciting and especially important in immunotherapy response."

That's one thing Delgoffe would like to see studied further. With the genetic signature from UPenn's Li and his team, scientists can try to design new experiments to see if the presence of mitochondrial robbers correlates with failure from immunotherapies in large datasets, Delgoffe said. "And you have to ask — is it a target? Is there something you can do to turn this thing off and prevent mitochondrial theft from occurring?"

When Li looked at what genes were turned on in the robber cancer cells, he found hundreds of genes that were more active compared to the non-robbers. Many of these genes are important in nanotube formation and elongation, as well as proteins involved in the construction of cellular skeletons. "That makes a lot of sense," Li said, considering the robbers must build a long nanotube tendril to reach out and ensnare immune cells.

That might create an opportunity for researchers to create a drug that inhibits the formation of these nanotubes, Li said, or find ways to harden T cells against the theft. An advance in either direction could help scientists take away one of cancer's greatest advantages over the immune system and boost immunotherapies for patients.

About the Author

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