Scientists discover cancer treatment two-and-a-half times more effective when tumors have defective mitochondria

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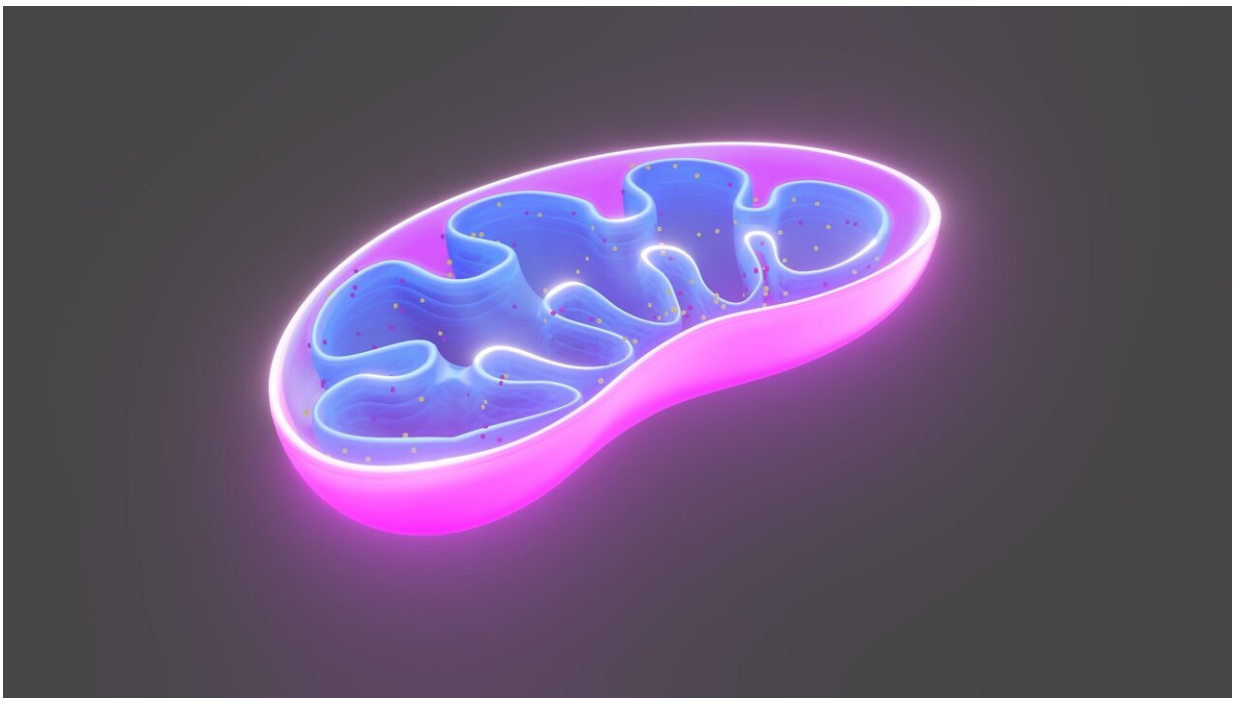

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Scientists have made an unusual discovery that could help to identify patients who are up to two-and-a-half times more likely to respond to currently available cancer drugs.

Scientists at the Cancer Research UK Scotland Institute and Memorial Sloan Kettering Cancer Center in the U.S. have "rewired" the DNA of mitochondria—energy factories found in every living cell. They found that creating mutations in parts of this DNA determines how well cancer will respond to immunotherapy—treatments that harness the body's natural defenses to attack cancer cells.

This discovery opens up new ways to identify patients who could benefit most from immunotherapy by testing for mitochondrial DNA mutations. Half of all cancers have mitochondrial DNA (mtDNA) mutations and this discovery shows for the first time that they could be exploited to improve cancer treatment.

In the future, combining treatments that mimic the effect of these mutations with immunotherapy could increase the chances of successful treatment for multiple types of cancer.

In a paper, titled "Mitochondrial DNA mutations drive aerobic glycolysis to enhance checkpoint blockade in melanoma," in *Nature Cancer* the scientists demonstrate for the first time a direct link between mitochondrial DNA (mtDNA) mutations and response to cancer treatment. Surprisingly, they found that tumors with high levels of mtDNA mutations are up to two and a half times more likely to respond to treatment with an immunotherapy drug called nivolumab.

Nivolumab works by releasing a "brake" on the immune system to attack cancer cells. It is currently used to treat several different cancers, including melanoma, lung cancer, liver cancer and bowel cancer. The scientists believe that they could routinely test for mitochondrial DNA mutations in the future—enabling doctors to figure out which patients will benefit most from immunotherapy before starting treatment.

They also believe that mimicking the effects of the mitochondrial DNA

mutations could make treatment-resistant cancers sensitive to immunotherapy—enabling thousands more cancer patients to benefit from this pioneering treatment.

The technology behind the discovery is now the subject of patents filed by Cancer Research Horizons, Cancer Research UK's innovation arm. It will help bring the technology to market to allow new treatments to be developed which disrupt the energy sources cancer uses to spread and grow. To date, Cancer Research Horizons has brought 11 new cancer drugs to market, which have been used in over six million courses of cancer treatment worldwide.

Group Leader at the Cancer Research UK Scotland Institute and the University of Glasgow and co-lead author of the study, Dr. Payam Gammage, said, "Cancer is a disease of our own bodies. Because cancer cells can look similar to healthy cells on the outside, getting our immune systems to recognize and destroy cancer cells is a complicated task.

"More than half of cancers have mutations in their mitochondrial DNA. But when we engineered these mutations in the lab, we found that tumors which have the most mutated mitochondrial DNA are far more sensitive to immunotherapy.

"Thanks to this research, we now have a powerful tool which gives us an entirely new approach to stopping cancer in its tracks."

Assistant Attending Computational Oncologist at Memorial Sloan Kettering Cancer Center and co-lead author of the study, Dr. Ed Reznik, said, "Mitochondrial DNA has been an enigma for decades. Every cell has thousands of copies and until now it's been very challenging to engineer mutations consistently to study how mtDNA mutations affect cancer.

"For the first time, we can see exactly what mitochondrial DNA mutations do when we create them in the lab. But what took us by surprise is how much the cells around the tumor are affected—which we can exploit to make the tumor vulnerable to treatment.

"This research opens up an entire world where we can rewire the energy sources of tumors—and potentially short-circuit them to beat cancer sooner."

Executive Director of Research and Innovation at Cancer Research UK and CEO of Cancer Research Horizons, Dr. Iain Foulkes, said, "After years of painstaking lab research..., we have identified a vital weak spot in cancer. Mitochondrial DNA mutations are a common part of cancer and this amazing discovery has limitless potential.

"Treatments which exploit over-burdened mitochondria in cancer are now possible. Now we need clinical trials to see which combinations work best in patients. Through our innovation engine Cancer Research Horizons, we're planning to accelerate this discovery into the clinic and ensure as many patients as possible can benefit."

More information: Mitochondrial DNA mutations drive aerobic glycolysis to enhance checkpoint blockade in melanoma, *Nature Cancer* (2024). DOI: 10.1038/s43018-023-00721-w

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