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Revealed: How cancer develops resistance to treatment

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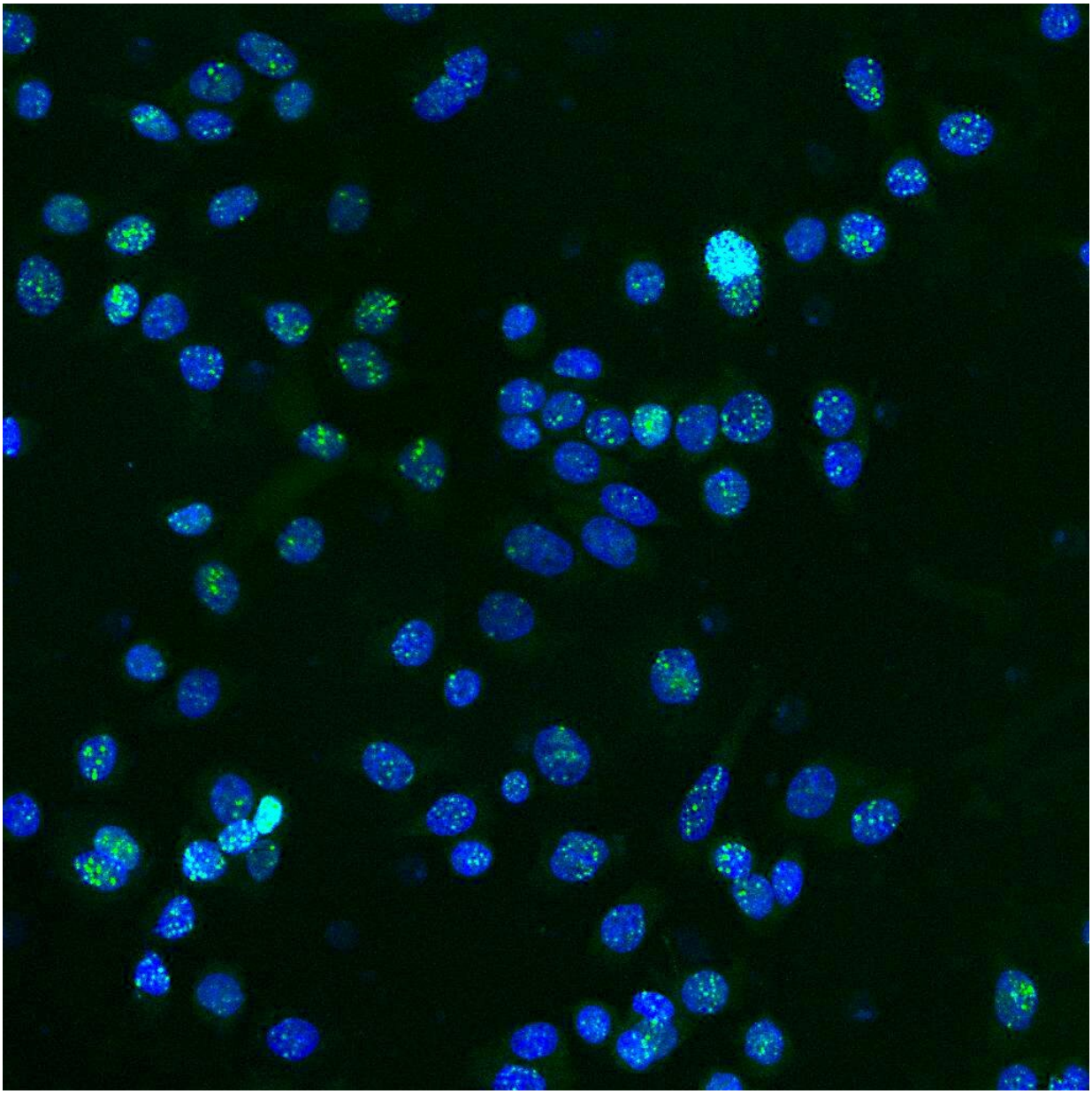

DNA damage accumulated by human breast cancer cells, in response to targeted anticancer agents. The genetic diversity generated during the processes of DNA repair facilitates adaptive evolution and therapeutic failure. Credit: Dr Arcadi Cipponi

Cancer cells can turn on error-prone DNA copy pathways to adapt to cancer treatment, a breakthrough study published in the journal *Science* has revealed. Bacteria use the same process, termed stress-induced mutagenesis, to develop antibiotic resistance.

The cells of the human body are constantly dividing, and each time need to copy a three billion-letter DNA code with high precision to ensure cell survival. The same is not true for cancers, researchers have discovered.

A team led by Professor David Thomas at the Garvan Institute of Medical Research has shown how a broad range of cancers, including melanoma, pancreatic cancer, sarcomas and breast cancer, generate a high number of errors when they copy their DNA when exposed to cancer treatments, leading to drug resistance.

"Resistance to treatment is arguably the major issue facing patients with advanced cancers, for whom even effective treatments ultimately fail. We have uncovered a fundamental survival strategy that cancer cells use to develop resistance, and which has given us new possible therapeutic strategies," says Professor Thomas, Garvan's Cancer Research Theme Leader and Director of The Kinghorn Cancer Centre.

Resisting cancer treatment

Resistance to cancer therapy affects hundreds of thousands of cancer patients every year, leading to devastating health outcomes even for the

most advanced treatments.

Researchers have long known that cancer cells accumulate genetic variations that make it possible for them to evade treatment. But how this happens—and whether the process could be targeted to improve cancer treatment—has been elusive.

The authors of the current study began to investigate the underlying drivers of treatment resistance by analyzing biopsy samples from cancer patients, before and after they were treated with targeted cancer therapies. Targeted therapies block the growth of cancer by interfering with molecules that are needed for tumor growth, and are a common treatment for many forms of cancer.

They were surprised to discover that the cancer cells from patients that had received targeted therapies showed much higher levels of DNA damage than pre-treatment samples—even when these treatments did not directly damage DNA. Further, the researchers used whole genome sequencing to analyze how treatment resulted in accelerated evolution of the cancer genome.

"Our experiments revealed that cancer cells exposed to targeted therapies undergo a process called stress-induced mutagenesis—they generate random genetic variation at a much higher rate than cancer cells not exposed to anti-cancer drugs," says first author Dr. Arcadi Cipponi.

"This process is ancient—single-celled organisms, such as bacteria, use the same process to evolve when they encounter stress in their environment."

Cancer's two-step strategy for resistance

To pinpoint the mechanisms underlying stress-induced mutagenesis in

human cancer cells, the researchers carried out a large-scale screen to silence every gene in cancer cells individually, looking to identify the specific pathways contributing to drug resistance.

When they silenced the gene for MTOR—a stress sensor protein—they discovered that cancer cells stopped growing, but paradoxically accelerated evolution in the presence of a cancer treatment.

"MTOR is a sensor protein that tells normal cells to stop growing because there is a stress in the environment. But we found that in the presence of a cancer treatment, MTOR signaling allowed cancer cells to change expression of genes involved in DNA repair and replication, for example shifting from high-fidelity polymerases, the enzymes that copy DNA, to production of error-prone polymerases," says Dr. Cipponi. "This resulted in more genetic variation, ultimately fuelling resistance to treatment."

The shift to low-fidelity DNA repair and replication was temporary—once cancer cells acquired resistance to a cancer treatment, they reactivated high-fidelity pathways.

"Genomic instability can itself be harmful to cells—which is why some of our chemotherapies and therapeutic radiation work. We found that once cancer cells had developed resistance to a treatment, they switched back to high-fidelity DNA polymerases to ensure the cells that had evolved resistance to treatment could survive," explains Dr. Cipponi.

New approach for cancer treatments

Combining conventional targeted cancer therapy with drugs that target DNA repair mechanisms, the researchers say, may lead to more effective therapeutic strategies.

As a proof-of-principle, the researchers tested such a drug combination in a mouse model of pancreatic cancer. By combining the cancer treatment palbociclib with rucaparib, a drug which selectively targets cells with impaired DNA repair, they were able to reduce cancer growth by almost 60% over 30 days, compared to palbociclib alone.

"Our findings have opened up new potential strategies that either prevent stress-induced mutagenesis in cancers, or are more effective in cancers that have already developed resistance," says Professor Thomas.

More information: "MTOR signaling orchestrates stress-induced mutagenesis, facilitating adaptive evolution in cancer" *Science* (2020). science.sciencemag.org/cgi/doi … 1126/science.aau8768

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