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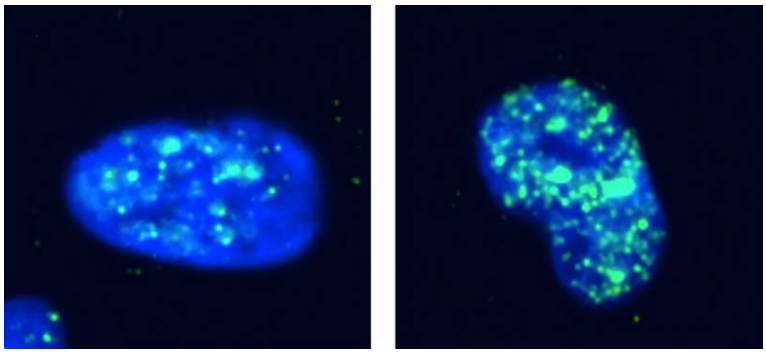
Study finds new weak spot linked to DNA repair in aggressive, drug-resistant cancers



When the researchers led by Nanyang Technological University, Singapore treated triple-negative breast cancer cells with PARP inhibitors and chemicals that induced DNA damage, some PARP1 enzymes (in green) were found on the cells' DNA (in blue) (left). But in cells where the TEX264 protein was blocked, more PARP1 molecules accumulated on the DNA (right). This suggests that TEX264 is involved in removing PARP1 from DNA. Credit: Adapted from Hoslett et al., Nature Cell Biology (2026), Jun;28(6):1219-1234. DOI: 10.1038/s41556-026-01961-5; licensed under CC BY 4.0

A new way for hard-to-treat cancer cells to protect themselves from being killed by anticancer drugs has been found. The novel method involves tumors hijacking specific defenses for repairing damaged DNA, which are easier to block than previously known mechanisms.

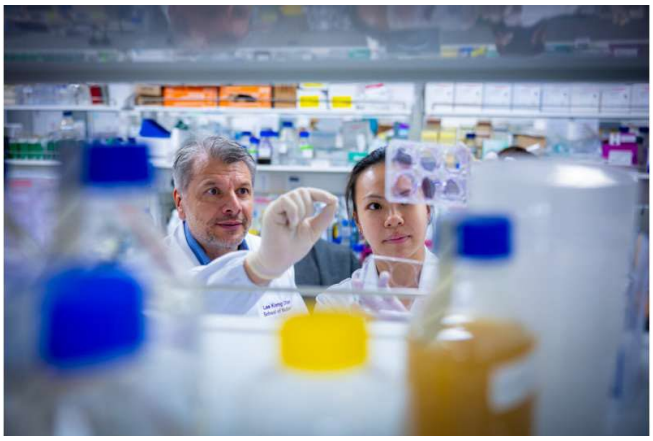
This finding from a team of international scientists led by Nanyang Technological University, Singapore (NTU Singapore), paves the way for addressing long-standing difficulties in fighting drug resistance.

For patients with breast, prostate, pancreatic or ovarian cancer whose tumor cells have lost a major ability to repair severe DNA damage, a class of anticancer drugs called poly-ADP-ribose polymerase (PARP) inhibitors has been approved to treat such conditions.

The drugs work by disrupting DNA repair processes in tumors, leading to a toxic level of DNA damage that causes cancer cells to die.

Yet some patients' tumors develop resistance to these drugs. About 40%–70% of ovarian and breast cancer patients develop this resistance. Various mechanisms for

how the resistance works have been discovered, but they are often hard to target with drugs that counter tumors' drug resistance.



Professor Kristijan Ramadan and PhD student Joanne Loh from Nanyang Technological University, Singapore checking cancer cells grown in culture plates. Researchers led by Prof Ramadan discovered that cancer cells can hijack and connect DNA repair and autophagy mechanisms to make them harder to kill with many drugs. Credit: NTU Singapore.

TEX264 emerges as a target

However, researchers led by Professor Kristijan Ramadan from NTU's Lee Kong Chian School of Medicine (LKCMedicine) discovered a new mechanism involved in PARP inhibitor resistance that could be treated with drugs. Their findings were published in *Nature Cell Biology*.

The scientists' experiments showed that cancer cells can use a protein called TEX264, which helps clear molecules that can cause DNA damage through a process called autophagy. By doing so, TEX264-initiated autophagy prevents PARP inhibitors from interfering with DNA repair. This protects cancer cells' DNA from further damage and helps them survive treatment with PARP inhibitors.

When TEX264's function was blocked, cancer cells developed 40%–110% more DNA damage across different damage indicators when treated with PARP inhibitors, thus reversing resistance to the drugs. Statistical analysis revealed that the cancer cells were more prone to dying.

The researchers also found a TEX264 link among patients. They analyzed clinical data from the Sweden Cancerome Analysis Network – Breast (SCAN-B) study, specifically 700 patients with triple-negative breast cancer, the most aggressive and hard-to-treat form of the disease. Among these patients, those with low levels of TEX264 had a 28% higher chance of survival over 10 years compared with patients with higher TEX264 levels.

Sara Tribble, a Ph.D. student from the University of Oxford's Department of Oncology and a co-author of the study, said, "The results suggest that TEX264 is a possible biomarker for predicting survival among patients with the most aggressive breast cancer subtype, triple-negative breast cancer with DNA repair deficiency, and could also guide more personalized treatments for them."

Ramadan added, "Our findings have identified a new biological process involving TEX264 as a key mechanism of drug resistance in an aggressive form of cancer. We coined this new biological mechanism 'autophagy of DNA lesions' or simply 'nucleophagy.' This makes TEX264 a potential target for cancer therapies."

Samples being loaded onto a confocal microscope. The microscope was used to visualize cancer cells in experiments led by Professor Kristijan Ramadan from Nanyang Technological University, Singapore. Credit: NTU Singapore

Clearing 'jams' on DNA

PARP inhibitors work by targeting a DNA repair enzyme called PARP1. When DNA gets damaged, it is like a road with cracks. One way to repair it is for PARP1 to bind to DNA where the lesion occurred, which is akin to a road repair vehicle moving to a damaged site. This acts as a signal to bring other DNA repair proteins to the damaged site to mend it. After the damage is repaired, PARP1 unbinds from and leaves the DNA.

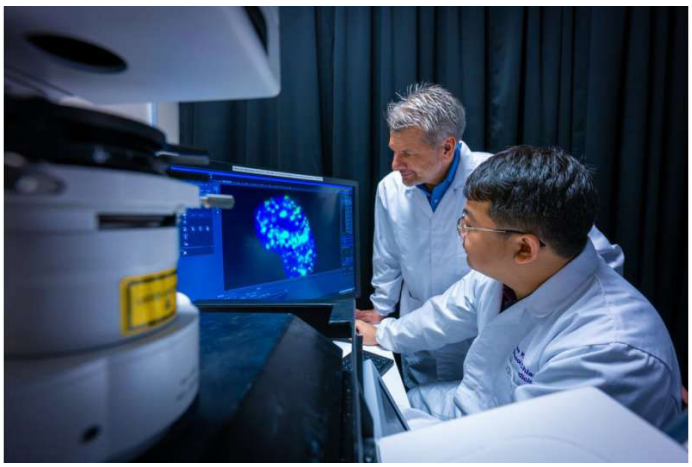
But PARP inhibitors prevent PARP1 from leaving, causing the enzyme to remain stuck on DNA. This is like causing a repair vehicle to stall and block the road, creating a traffic jam. Other molecules, such as those involved in creating copies of DNA, may crash into this "traffic jam" and cause further, more deleterious DNA damage. If this happens, the cancer cell can no longer cope with the amount of DNA damage and dies.

The cell has defenses against this, however. When a jam is detected on DNA, the protein TEX264 helps direct processes that clear the jam. This includes removing and

destroying PARP1 stuck on the DNA, a process called nucleophagy that clears "junk" from a cell's nucleus.

This ability of TEX264 to remove PARP1 trapped on DNA by PARP inhibitors was discovered by NTU-led scientists in cancer cells that can hijack DNA repair mechanisms, making them difficult to kill with many drugs.

For example, one series of experiments showed that the use of PARP inhibitors resulted in a 40% increase in TEX264 binding to PARP1. The finding was supported by experiments that blocked autophagy, a process for clearing and destroying "cellular junk," in cancer cells. This resulted in about 70% more PARP1 being found on the cells' DNA.



Kristijan Ramadan and Research Fellow Li Dong from Nanyang Technological University, Singapore observing a cancer cell visualized by a confocal microscope. Prof Ramadan led experiments to show how cancer cells hijack DNA repair mechanisms to make them harder to kill with drugs. Credit: NTU Singapore.

Why the findings resonate locally

There was also more DNA damage and tumor cell death. A scientist from LKCMedicine, Dr. Alvin Wei Tian Ng, also discovered a link between TEX264 levels and the odds of survival among patients in Sweden with the most aggressive form of breast cancer.

The findings suggest that in aggressive triple-negative breast cancer, tumor cells subvert the DNA repair and autophagy functions of TEX264 to protect themselves from being killed by PARP inhibitor treatment.

The results are relevant for Singapore because triple-negative breast cancer is highly prevalent in the country's population.

Earlier studies have found that, compared with other populations worldwide, Singaporeans have a roughly three times higher occurrence of defects in genes involved in DNA repair, a hallmark of about half of all triple-negative breast and ovarian cancers.

Around 1 in 150 Singaporeans is a carrier of mutations in DNA repair genes linked to breast and ovarian cancers, compared with about 1 in 400–500 people globally.

Clinical Assistant Professor Tira J. Tan, a senior consultant in the Division of Medical Oncology at the National Cancer Centre Singapore who was not involved in the study, said, "Resistance to PARP inhibitors is one of the biggest challenges we face in the clinic when treating cancer. Until now, it was widely understood that most known resistance mechanisms center on the tumor restoring its DNA repair capacity or pumping PARP inhibitor drugs out of cancer cells."

The NTU-led study is important because it reveals a completely different resistance mechanism that cancer cells can use to "clean up" the drug-induced damage meant to kill them, said Tan, who specializes in breast cancer and early-phase drug development.

Testing combination treatments next

"By identifying the nucleophagy pathway and the key proteins involved, this study points to new strategies where PARP inhibitors can be paired with drugs that block the resistance pathway to deepen response to treatment," she added.

Going forward, clinical studies are needed to validate these findings in human patients. This can be achieved by investigating whether drugs that block TEX264-dependent autophagy of DNA damage—such as chloroquine or hydroxychloroquine, both clinically approved autophagy inhibitors—can be used in combination with PARP inhibitors to treat aggressive cancers that are hard to treat and have developed drug resistance.

"Our findings highlight the potential for combination therapies and provide a strong rationale for future clinical trials," Ramadan said. "We are now seeking clinical partners, donors and venture capitalists to help translate this discovery into clinical application."

https://medicalxpress.com/news/2026-07-weak-linked-dna-aggressive-drug.html