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Singapore-led study identifies DNA repair weak spot in drug-resistant cancers

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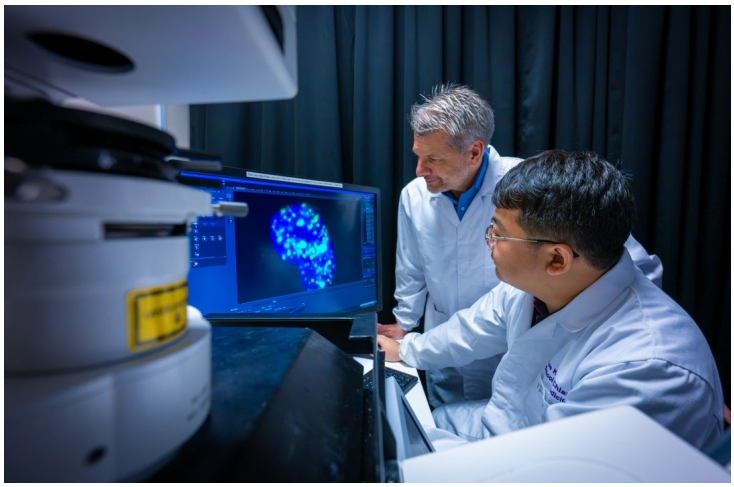
The findings suggest that TEX264, a protein linked to autophagy and DNA repair, may play a role in PARP inhibitor resistance among hard-to-treat cancers.



A new way for hard-to-treat cancer cells to protect themselves from being killed by anti-cancer drugs has been found. The novel method involves tumours hijacking specific defences for repairing damaged DNA, which was found to be 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 with fighting this drug resistance.

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

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

Yet some patients' tumours develop resistance to these drugs. About 40 to 70 per cent 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 to counteract the tumours' drug resistance.

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 holds potential to 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 by a process called autophagy. By doing so, TEX264-initiated autophagy prevents PARP inhibitors from interfering with DNA repair. This protects cancer cells' DNA from being further damaged and helps them

survive cancer treatment with PARP inhibitors.

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

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

Sara Tribble, a PhD 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 the most aggressive subtypes of breast cancers, triple-negative breast cancer patients with DNA repair deficiency, and could also guide more personalised treatments for them."

Prof 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 just simply 'nucleophagy'. This makes TEX264 a potential target for cancer therapies."

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 has happened, which is akin to a road repair vehicle moving to the damaged site on the road. 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 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 and 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 defences against this, however. When a jam is detected on DNA, the protein TEX264 helps to direct processes that clear up the jam. This includes removing and destroying PARP1 stuck on the DNA, a process called nucleophagy for clearing "junk" from a cell's nucleus.

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

For example, one series of experiments showed that the use of PARP inhibitors resulted in a 40 per cent increase in TEX264 binding to PARP1. The finding is complemented by experiments that blocked a process for clearing and destroying "cellular junk" called autophagy in cancer cells, which resulted in more PARP1 found on the cells' DNA, about 70 per cent more. There was also more DNA damage and tumour cell death.

The findings suggest that in aggressive triple-negative breast cancers, the tumour cells subvert the DNA-repairing and autophagy function of TEX264 to protect themselves from getting killed by PARP inhibitor treatment.

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

Earlier studies have found that, compared to other populations in the world, 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 to about 1 in 400 to 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 latest 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 centre on the tumour 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 Dr Tan, who specialises in breast cancer and early phase drug development.

“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,” said Prof Ramadan. “We are now seeking clinical partners, donors and venture capitalists to help translate this discovery into clinical application.”