

NTU study could offer clues to overcoming cancer drug resistance

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The Straits Times, Prime, Page 4, Section: THE BIG STORY
Monday 28 September 2026
697 words, 495cm² in size
386,100 circulation



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Research by scientists from the Nanyang Technological University (NTU) has uncovered how tumours can hijack DNA repair mechanisms to resist anti-cancer drugs, as well as how this drug resistance can be reversed.

In patients with breast, ovarian, pancreatic or prostate cancers linked to mutations that affect DNA repair, poly-ADP-ribose polymerase (PARP) inhibitors are used to block PARP enzymes, which cancer cells use to repair their DNA.

When these enzymes are disrupted, DNA damage builds up to toxic levels, causing the cancer cells to die.

However, in some patients, tumours develop resistance to these drugs, with between 40 and 70 per cent of patients with breast or ovarian cancer showing such resistance.

While various mechanisms for how this resistance works have been discovered, they have often been hard to target.

Now, a team of researchers from NTU has discovered how cancer cells use a protein called TEX264 to clear molecules that cause DNA damage via autophagy, or the degradation of damaged cellular components.

The team is led by Kristijan Ramadan, a professor of cancer and stem cell biology at the NTU Lee Kong Chian School of Medicine.

This autophagy helps cancer cells resist PARP inhibitors, protecting their DNA from further damage and thus helping them survive.

Research discovered that blocking TEX264 functions resulted in cancer cells developing between 40 and 110 per cent more DNA damage when treated with PARP inhibitors.

The researchers also analysed clinical data from the Sweden Cancerome Analysis Network – Breast study.

The Swedish study involved more than 23,000 breast cancer patients, with the aim of integrating genomic profiling into clinical care – specifically looking at 700 patients with triple-negative breast cancer, which is particularly aggressive and hard to treat.

They found that patients with low levels of TEX264 had a 28 per cent higher 10-year survival rate than those with higher levels of the protein.

Their findings were published in the peer-reviewed scientific journal Nature Cell Biology in June.

“The results suggest that TEX264 is a possible biomarker

for predicting survival among the most aggressive subtypes of breast cancer, (including) triple-negative breast cancer patients with DNA repair deficiency, and could also guide more personalised treatments for them,” said Sara Tribble, a PhD student from the University of Oxford’s oncology department, who is one of the study’s co-authors.

WHY THE FINDINGS MATTER IN SINGAPORE

The new biological process uncovered – with TEX264 as a key drug resistance mechanism – has been dubbed “nucleophagy”, said Ramadan.

In the longer term, with more investment and a greater focus on research, the findings could be used to develop “clever drugs” that better target TEX264, he added.

Tira Tan, a senior consultant at the National Cancer Centre Singapore’s medical oncology division, noted that while most known resistance mechanisms centre on tumours restoring their DNA repair capacity or pumping PARP inhibitor drugs out of cancer cells, the NTU-led study reveals a completely different type of resistance mechanism.

“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 improve response to treatment,” said Tan, who was not involved in the study.

Ramadan told The Straits Times that the findings were particularly relevant in Singapore, where the occurrence of BRCA gene mutations is three times higher than in other populations.

Cancer cells with BRCA mutations – linked to a higher risk of breast cancer, in particular triple-negative breast cancer – are targeted with PARP inhibitors.

Ramadan noted that one in 150 Singaporeans has a gene mutation that significantly raises their risk of developing cancers such as breast, ovarian, pancreatic or prostate cancer.

The findings could allow for the development of biomarkers to determine which patients have higher levels of TEX264, allowing doctors to make better-informed decisions on therapies, said Ramadan.

“We really want to understand this process better. We want to see whether this is only for triple-negative breast cancer, or (whether) this model can also be applied for different types of cancer,” he said.

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NTU Lee Kong Chian School of Medicine’s Kristijan Ramadan (left), who led the study, and PhD student Joanne Loh checking cancer cells in culture plates.
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