Damaged DNA in Colorectal Cancer Chemo Patients Might Be Repaired More Effectively with New Therapy

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An international research team from the University of Oxford and Nanyang Technological University (NTU Singapore) reports the discovery of a new process for repairing damaged DNA that is particularly relevant for patients undergoing colorectal cancer treatments.

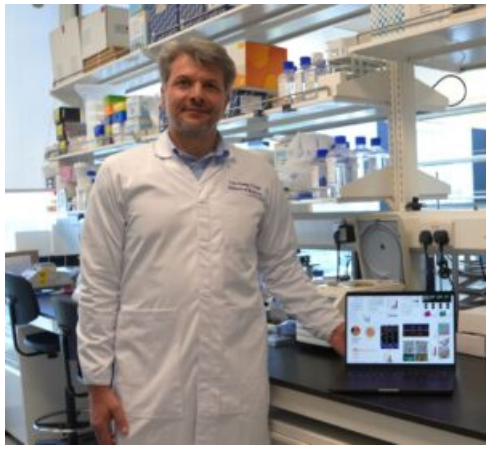
The study "TEX264 drives selective autophagy of DNA lesions to promote DNA repair and cell survival" in *Cell* describes how cells remove harmful DNA-protein lesions from a cell's nucleus, ensuring the stability of their genetic material and promoting cell survival. The team calls this new process nucleophagy, a natural cellular cleaning mechanism (autophagy) that is essential for repairing DNA and ensuring cell survival. It involves a commonly expressed protein called TEX264.

"DNA repair and autophagy are distinct biological processes vital for cell survival. Although autophagy helps maintain genome stability, there is no evidence of its direct role in the repair of DNA lesions. We discovered that lysosomes process topoisomerase 1 cleavage complexes (TOP1cc) DNA lesions in vertebrates," write the investigators.

Selective degradation
"Selective degradation of TOP1cc by autophagy directs DNA damage repair and cell survival at clinically relevant doses of topoisomerase 1 inhibitors. TOP1ccs are exported from the nucleus to lysosomes through a transient alteration of the nuclear envelope and independent of the proteasome.

"Mechanistically, the autophagy receptor TEX264 acts as a TOP1cc sensor at DNA replication forks, triggering TOP1cc processing by the p97 ATPase and mediating the delivery of TOP1cc to lysosomes in an MRE11-nuclease- and ATR-kinase-dependent manner. We found an evolutionarily conserved role for selective autophagy in DNA repair that enables cell survival, protects genome stability, and is clinically relevant for colorectal cancer patients."

In a patient receiving chemotherapy for colorectal cancer, the drugs cause DNA lesions to form. In response, the body expresses TEX264, which activates the nucleophagy process, guiding the lesions to the cell's waste disposal system, where they are broken down and destroyed.



Kristijan Ramadan, PhD, lead investigator, Lee Kong Chian School of Medicine

The research team used biochemical, cell biological and bioinformatics tools, a zebrafish animal model, and colorectal cancer patient materials to confirm that nucleophagy is crucial for repairing damaged DNA.

This study provides insights into a new pathway for cells to repair DNA damage, which could improve cancer treatments and lead to better outcomes for patients in the future, according to the research team, which comprises scientists and clinicians.

"While autophagy is known to be associated with DNA repair, there has been no evidence of its direct role in the repair of DNA lesions until now," said Kristijan Ramadan, PhD, lead investigator and the Toh Kian Chui Distinguished

“Our discovery that nucleophagy plays a direct role in DNA repair of chemotherapy-induced lesions is the result of a five-year joint effort among several laboratories in the U.K., Singapore, U.S., Portugal and Croatia,” added Ramadan, who is also a medical research council investigator at the department of oncology, University of Oxford.

In particular, the research team says the findings are significant for patients with colorectal cancer, the second leading cause of cancer-related deaths worldwide, according to the World Health Organization.

An analysis of colorectal cancer patients treated with Topoisomerase 1 inhibitors, such as FOLFIRI therapy (a common chemotherapy used to treat colorectal cancer), showed that patients with high levels of TEX264 in their tumors have a 50 percent better response to treatment compared to those with low levels of TEX264.

In future studies, the research team will explore the role of nucleophagy in the body’s response to chemotherapeutic drugs for other cancers to see if their discovery is further validated. The team’s ultimate goal is to use their work to improve current chemotherapy responses for cancer patients.

News | Autophagy | Chemotherapy | Colorectal cancer | DNA damage (Biological process) | DNA repair | Lysosome