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JULY 21, 2025

How cells repair toxic DNA damage linked to cancer and premature aging

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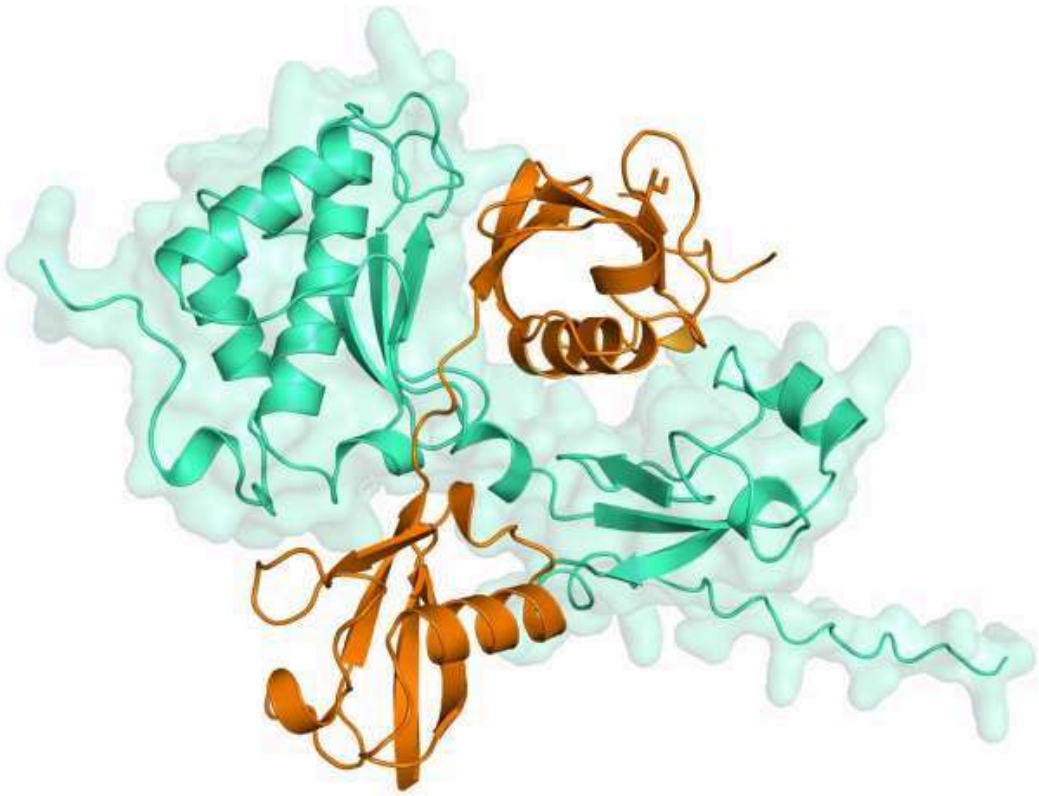

An artificial intelligence-predicted image of a region in the SPRTN enzyme (green structure) that can recognise and bind to ubiquitin chains (orange structure). Credit: University of Oxford)

Researchers at the University of Oxford and Nanyang Technological University, Singapore (NTU Singapore) have uncovered the mechanism by which cells identify and repair a highly toxic form of DNA damage that causes cancer, neurodegeneration, and premature aging.

The findings, published in *Nucleic Acids Research*, reveal how DNA-protein crosslinks (DPCs)—harmful DNA lesions induced by chemotherapy, formaldehyde, and UV exposure—are recognized and broken down by SPRTN, a key repair enzyme.

The research team discovered a new region within SPRTN that enables it to selectively target DPC lesions, increasing its repair activity 67-fold while leaving surrounding structures unharmed.

Led by Kristijan Ramadan, Toh Kian Chui Distinguished Professor in Cancer and Stem Cell Biology at the Lee Kong Chian School of Medicine, NTU Singapore and Honorary Senior Researcher at the Department of Oncology, University of Oxford, the work has important implications for improving cancer therapy and healthy aging.

The threat of DPC lesions

Every time a cell divides into two, it must accurately create a copy of all its DNA, a process that involves the tight coordination of sophisticated molecular machinery. DNA-protein crosslinks (DPCs) are bulky lesions in which unwanted proteins attach to DNA, blocking the process of copying the cell's DNA.

If left unrepaired, DPCs can cause neurodegeneration, premature aging, and cancer. Therefore, understanding how these lesions are repaired is crucial for protecting genome integrity and preventing these conditions.

DPCs can occur through normal cellular metabolism, as well as exposure to chemotherapeutic drugs, UV radiation, and environmental agents like formaldehyde. Formaldehyde is a Group 1 carcinogen commonly found in household furniture, paint, and air pollution, including haze.

SPRTN is a critical enzyme that protects cells against DPC lesions. It travels along the DNA and degrades the proteins in the lesions, which clears the blockage and enables the DNA copying process to proceed.

Until now, it was unknown how SPRTN specifically breaks down DPC lesions without damaging functional proteins in the cell.

Discovery of a damage recognition domain

The research team discovered a specialized region within SPRTN which drives its activity against DPCs. The region detects chains of ubiquitin—tiny tags that attach to other proteins to modify their function—which DPC lesions have in abundance.

Recognition of these tags directly guides SPRTN to the DPC lesions, triggering a rapid increase in its activity to break down the harmful protein attachments.

"In the absence of ubiquitin chains on DPCs, SPRTN is slow and inefficient, taking hours to clear the DNA lesions. But when the ubiquitin chains are present, SPRTN's ability to specifically target DPCs and break them down is enhanced 67-fold, enabling rapid removal of DPCs, which is critical due to its role in the rapid repair of DNA," said Prof Ramadan, who is also the Director of the Cancer Discovery and Regenerative Medicine Program at NTU Singapore's Lee Kong Chian School of Medicine.

Importantly, the team showed that longer chains significantly accelerated the repair process compared to when only one or two ubiquitin tags were attached to the DNA lesion. This allows SPRTN to act quickly on DPCs while sparing other proteins that lack these tags.

Implications for cancer therapy and healthy aging

These findings, which demonstrate the importance of the newly discovered SPRTN region for DPC lesion repair, have important implications in cancer therapy and healthy aging.

Mutations in the SPRTN gene are known to cause Ruijs-Aalfs syndrome (RJALS), a rare condition characterized by chromosomal instability, premature aging, and a high risk of early-onset liver cancer. The discovery of SPRTN's recognition mechanism provides essential insights into our cells' natural defenses and how defects in DPC repair can drive disease.

First author of the study, Oxford's postdoctoral researcher Dr. Wei Song, said, "Our body's ability to repair DNA damage caused by DPCs has long been a mystery. But now that we know how the repair mechanism works, we've laid the groundwork for developing potential ways to strengthen the body's defenses against age-related diseases, as well as reduce the side effects of cancer therapies that damage DNA."

Commenting as an independent expert, Dr. Jens Samol, Senior Consultant in Medical Oncology, Department of Medical Oncology, Tan Tock Seng Hospital, Singapore, said that the researchers' study is significant as it identified that ubiquitin chains act as the main signal for SPRTN's rapid activation and are very likely the main signal for SPRTN to specifically target and break down DPCs heavily tagged with ubiquitin.

"These findings further the understanding of SPRTN's ability to specifically degrade DPCs and prevent normal cells from becoming cancerous," added Dr. Samol. "Moreover, some cancer patients are resistant to chemotherapy that kills tumor cells by inducing DPCs in them."

"The involvement of ubiquitin shown by the study opens the possibility of investigating whether anti-ubiquitin antibodies or ubiquitin-proteasome inhibitors, such as bortezomib, could potentially be used as therapeutic options for overcoming cancer patients' resistance to chemotherapy drugs. This concept could be tested in animal models like mice."

Future studies by the researchers, including ongoing work in zebrafish, mouse models and human tissues, aim to validate their findings and further explore the potential of strengthening DPC repair mechanisms. This research could further revolutionize our understanding of the processes of aging and cancer, as well as identify potential therapeutic interventions.

More information: Wei Song et al, The dual ubiquitin binding mode of SPRTN secures rapid spatiotemporal proteolysis of DNA–protein crosslinks, *Nucleic Acids Research* (2025). DOI: 10.1093/nar/gkaf638

Journal information: Nucleic Acids Research

Provided by Nanyang Technological University