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English translation

Study identifies mechanism that helps prevent cancer, neurodegeneration and premature aging

Researchers from the University of Oxford and Nanyang Technological University, Singapore (NTU Singapore) have revealed 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 Acid Research, reveal how DNA-protein cross-links (DPCs) — the harmful DNA damage 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 allows 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 ageing.

The threat of DPC injuries

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

If left unrepaired, DPCs can cause neurodegeneration, premature aging, and cancer. Therefore, understanding how these lesions are repaired is crucial to protect the integrity of the genome and prevent these conditions.

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

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

Until now, it was not known how SPRTN specifically breaks down DPC lesions without damaging functional proteins in the cell.

Discovery of a damage recognition area

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

Recognition of these tags directly guides SPRTN to the DPC damage, triggering a rapid increase in its activity to break down 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 Programme at the Lee Kong Chian School of Medicine in NTU Singapore.

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 stripping off other proteins that don't have these tags.

Implications for cancer therapy and healthy aging

These results, which demonstrate the importance of the newly discovered SPRTN region for the repair of DPC lesions, have important implications for 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 an anticipated high risk of liver cancer. The discovery of the mechanism of recognition of SPRTN provides essential information about the natural defenses of our cells and how defects in DPC repair can stimulate disease.

The study's first author, Oxford 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 boost the body's defenses against age-related diseases.”

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 primary signal for rapid activation of SPRTN and are most likely the primary signal for SPRTN to specifically target and break down DPCs that are tagged with ubiquitin.

“These findings increase the understanding of SPRTN’s ability to specifically degrade DPCs and prevent normal cells from becoming cancerous. In addition, some cancer patients are resistant to chemotherapy that kills tumor cells by inducing DPCs.

“The ubiquitin implication shown by the study opens up the possibility of investigating whether anti-ubiquitin antibodies or ubiquitin-proteasome inhibitors, such as bortezomib, could potentially be used as therapeutic options to overcome cancer patient resistance to chemotherapy drugs. This concept could be tested in animal models such as mice.”
- Dr. Jens Samol, Senior Consultant in Medical Oncology, Department of Medical Oncology, Tan Tock Seng Hospital, Singapore

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 to strengthen the DPC repair mechanisms. This research could further revolutionize our understanding of aging and cancer processes, as well as identifying potential therapeutic interventions.

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