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English text

Mechanism discovered to prevent cancer, neurodegeneration and premature aging

A recent study by researchers from the University of Oxford and Nanyang Technological University, Singapore (NTU Singapore) has uncovered the mechanism by which cells identify and repair a toxic form of DNA damage that can lead to cancer, neurodegeneration and premature aging. The groundbreaking discovery, published in *Nucleic Acids Research*, provides new insights into how DNA lesions, known as DNA-protein crosslinks (DPCs), are repaired by the enzyme SPRTN, with significant implications for anti-cancer therapies and healthy aging.

Background
DNA-protein lesions (DPCs) are bulky lesions that form when proteins attach to DNA, blocking its copying process during cell division. These lesions can occur as a result of normal cellular metabolism, but also due to exposure to chemotherapy drugs, UV radiation, and environmental agents such as formaldehyde. DPCs, if not repaired, can cause neurodegeneration, premature aging, and cancer.

About the current study
The researchers discovered a specialized region within SPRTN that allows for selectivity in repairing DPC lesions, increasing its activity by 67-fold without affecting surrounding structures. This region detects ubiquitin chains (small molecules that attach to proteins to modify their function), which are abundant in DPC lesions, guiding SPRTN to these lesions and rapidly activating repair mechanisms.

Results
In the absence of ubiquitin chains on DPCs, SPRTN has a slow and inefficient activity, requiring hours to clean up DNA lesions. However, when ubiquitin chains are present, SPRTN's ability to target and degrade DPCs is enhanced 67-fold, allowing for rapid clearance of DNA lesions, crucial for their rapid repair.

The researchers also demonstrated that longer ubiquitin chains significantly accelerate the repair process compared to short chains, allowing SPRTN to act rapidly on DPCs while protecting normal proteins that lack these tags.

Implications for cancer therapies and healthy aging
This discovery has important implications for cancer therapy and healthy aging, as mutations in the SPRTN gene are known to cause Ruijs-Aalfs syndrome (RJALS), a rare condition associated with chromosomal instability, premature aging, and an increased risk of early-onset liver cancer. Identifying this mechanism of DPC damage recognition provides essential insight into the natural defenses of cells and how defects in DPC repair can lead to disease.

Future studies
The researchers will continue to validate their findings using zebrafish models, mouse models, and human tissues, further exploring the potential for enhancing DPC repair mechanisms. These studies could revolutionize our understanding of aging and cancer and lead to the identification of innovative therapeutic interventions.

Conclusion
The findings in this study represent an important step in the development of more effective therapies for aging-related diseases and cancer. By understanding how cells repair DNA-protein damage and by harnessing this mechanism in future therapies, researchers hope to improve existing treatments and develop new approaches for the prevention and treatment of neurodegenerative diseases and cancer.

References
Song, W., et al. (2025). The dual ubiquitin binding mode of SPRTN secures rapid spatiotemporal proteolysis of DNA–protein crosslinks. Nucleic Acids Research. https://doi.org/10.1093/nar/gkaf638

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