Trapping DNA damage: Untangling the proteins that trigger some cancerous tumors

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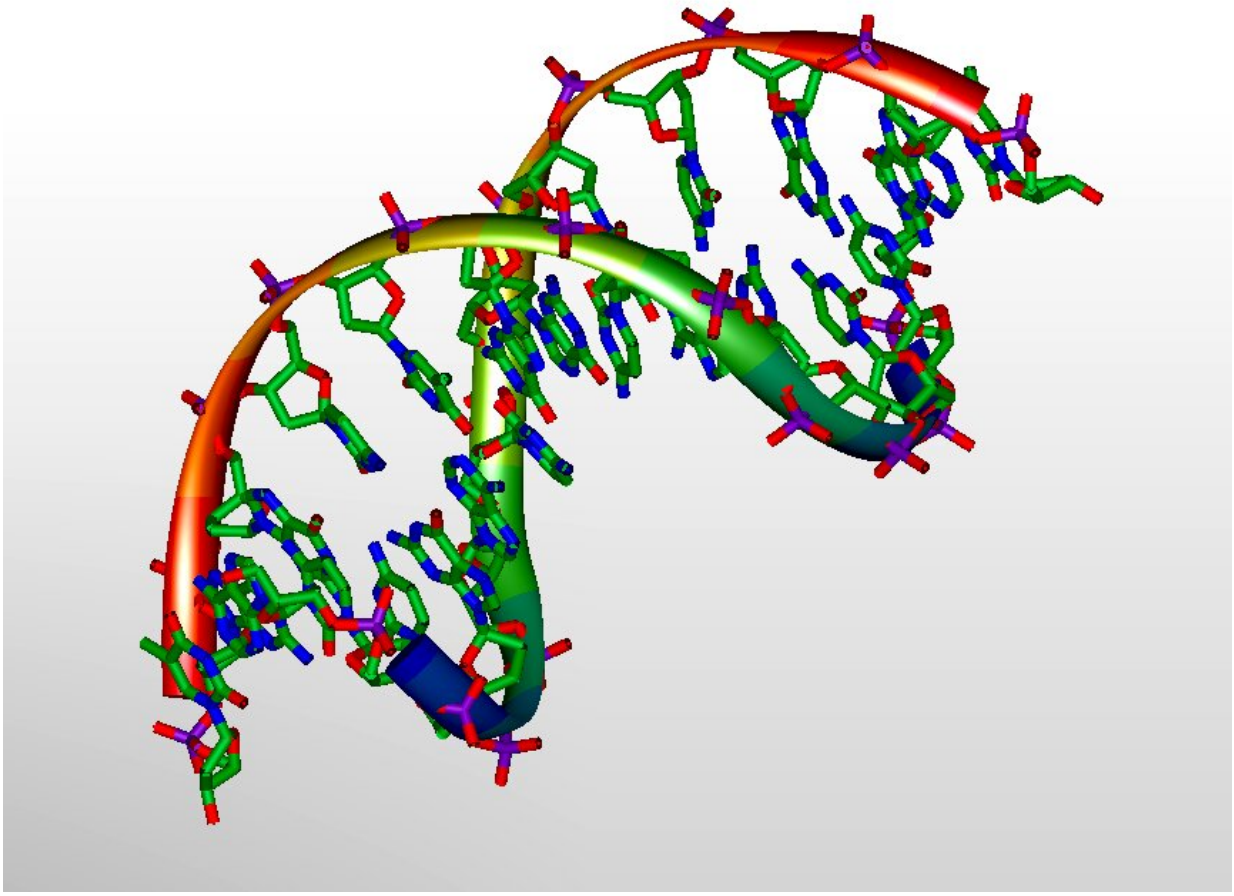

3D-model of DNA. Credit: Michael Ströck/Wikimedia/ GNU Free Documentation License

Even on a good day, DNA is constantly getting damaged.

Nicks, scratches, breaks: the delicate strands that carry life's genetic code take a beating as they jumble about in the course of their work. If left untreated, errors accumulate, with fatal consequences—such as cancerous tumors—for the cell and the organism.

This is where two key proteins come to the rescue: *PARP*—or poly ADP ribose polymerase—acts as a marker for a trouble spot, allowing *XRCC1*—or X-ray repair cross-complementing protein 1—to zoom in and begin a repair.

This much has been known for some time and was even recognized in the 2015 Nobel prizes for chemistry, resulting in the development of anti-cancer drugs known as *PARP inhibitors* that work to disrupt the growth of certain types of tumors.

But while these actors had been identified, their precise roles were not clear. Now a team of scientists at Tokyo Metropolitan University, the University of Sussex, and Kyoto University have revealed exactly how XRCC1 does its work.

"PARP turns out to be something of a villain," explains Kouji Hirota at Tokyo Metropolitan. "The spots it marks become 'PARP traps', which left un-repaired lead to disfunction and cell death."

XRCC1 therefore isn't simply repairing DNA, it is disarming PARP traps.

The scientists compared cells lacking the XRCC1 gene with those lacking PARP as well as with still others lacking both proteins. The team discovered that without XRCC1 on patrol, PARP traps accumulate like landmines.

"PARP exerts toxic effects in the cell and XRCC1 suppresses this toxicity," Hirota elaborates.

The team next seeks to delve even further into these processes, aiming to aid in the development of future cancer treatments.

KyotoU's Shunichi Takeda says that "these results indicate that XRCC1 is a critical factor in the resolution of PARP traps and may be a determinant of the therapeutic effect of PARP inhibitors used in the treatment of hereditary breast and ovarian cancer syndromes."

More information: Annie A. Demin et al, XRCC1 prevents toxic PARP1 trapping during DNA base excision repair, *Molecular Cell* (2021). DOI: 10.1016/j.molcel.2021.05.009

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