Building bridges: PARP enzymes bring broken DNA together

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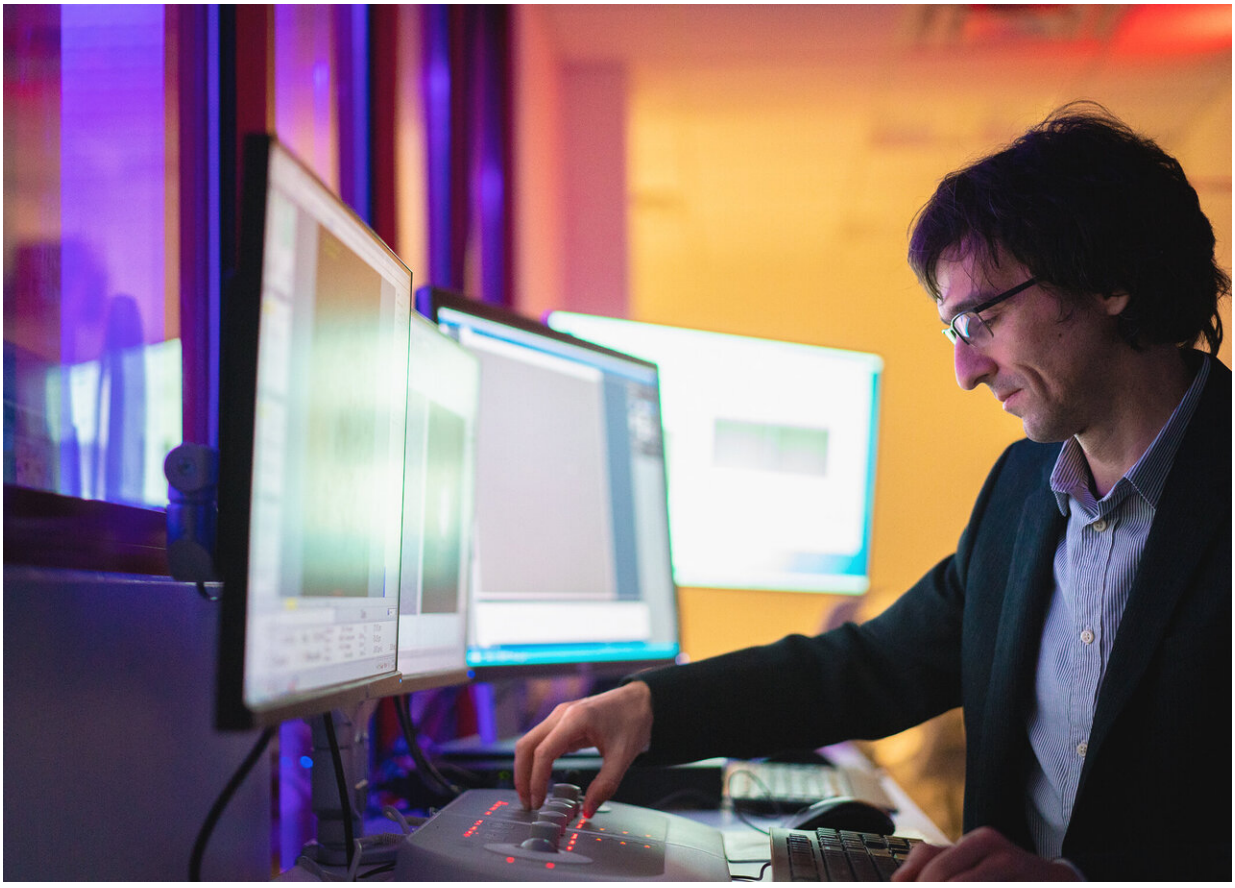

Mario Halic, Ph.D., of St. Jude Structural Biology. Credit: St. Jude Children's Research Hospital

Scientists at St. Jude Children's Research Hospital have identified the

structure of double-strand DNA break repair by PARP enzymes. The findings show that PARP2 can bridge the gap, bringing two broken DNA ends together.

The study also provides insight into the mechanisms that underlie PARP activation and the catalytic cycle, which may aid in understanding resistance to cancer drugs that inhibit PARP. The work appears as an advance online publication today in *Nature*.

"We expected that PARP would bind to DNA and modify chromatin to recruit other DNA repair factors," said corresponding author Mario Halic, Ph.D., of St. Jude Structural Biology. "Quite unexpectedly, we found that the PARP enzyme itself is bringing two broken DNA ends together."

DNA is constantly damaged and repaired. This can be naturally occurring or due to exposure to DNA damaging agents like some chemotherapies used to treat cancer. PARP is a family of enzymes known by scientists to be involved in several key cellular processes including DNA repair. However, exactly how PARP inhibitors interact with DNA and chromatin to accomplish this process was unknown.

The researchers used cryogenic electron microscopy to capture the structure of the PARP enzymes bound to DNA. Their findings showed that the enzyme can draw the ends of broken DNA together. The study may have important implications for understanding resistance to drugs that inhibit the activity of PARP.

PARP inhibitors are a class of drugs used to treat breast, ovarian and prostate cancers among others. These drugs work by stopping PARP enzymes from repairing DNA that has been damaged by chemotherapy. By stopping DNA repair, the drugs can help facilitate cancer cell death. Unfortunately, currently available PARP inhibitors are subject to

resistance.

"We now have a better understanding of the complex role PARP enzymes play in DNA repair," said first author Silvija Bilokapic, Ph.D., of St. Jude Structural Biology. "The mechanisms of PARP activation and catalytic cycle we identified help explain how resistance to PARP inhibitors occurs and could help in the development of more effective cancer treatments."

More information: Bridging of DNA breaks activates PARP2–HPF1 to modify chromatin, *Nature* (2020). DOI: 10.1038/s41586-020-2725-7 , www.nature.com/articles/s41586-020-2725-7

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