Study shows great specificity of action by enzymes to correct double-strand DNA breaks

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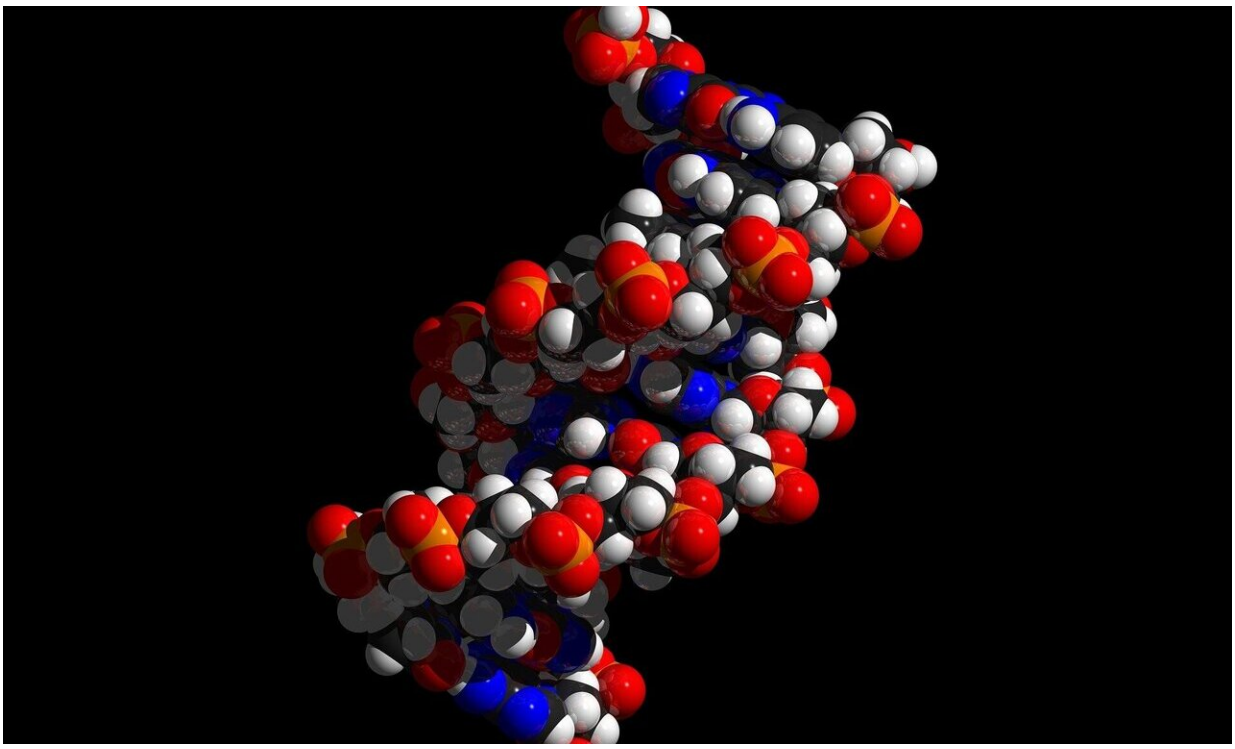

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Our cells are constantly dividing, and as they do, the DNA molecule—our genetic code—sometimes gets broken. DNA has twin strands, and a break in both is considered especially dangerous. This

kind of double-strand break can lead to genome rearrangements that are hallmarks of cancer cells, said James Daley, Ph.D., of the Long School of Medicine at The University of Texas Health Science Center at San Antonio.

Dr. Daley is first author of research, published June 18 in the journal *Nature Communications,* that sheds light on a double-strand break repair process called homologous recombination. Joined by senior authors Patrick Sung, DPhil, and Sandeep Burma, Ph.D., and other collaborators, Dr. Daley found that among an array of mechanisms that initiate homologous recombination, each one is quite different. Homologous recombination is initiated by a process called DNA end resection where one of the two strands of DNA at a break is chewed back by resection enzymes.

"What's exciting about this work is that it answers a long-held mystery among scientists," Dr. Daley said. "For a decade we have known that resection enzymes are at the forefront of homologous recombination. What we didn't know is why so many of these enzymes are involved, and why we need three or four different enzymes that seem to accomplish the same task in repairing double-strand breaks."

An array of tools, each one finely tuned

"On the surface of it, there seems to be quite a bit of redundancy," said Dr. Sung, who holds the Robert A. Welch Distinguished Chair in Chemistry at UT Health San Antonio. "Our study is significant in showing that the perceived redundancy is really a very naïve notion."

DNA resection pathways actually are highly specific, the findings show.

"It's like an engine mechanic who has a set of tools at his disposal," Dr. Sung said. "The tool he uses depends on the issue that needs to be

repaired. In like fashion, each DNA repair tool in our cells is designed to repair a distinctive type of break in our DNA."

The research team studied complex breaks that featured double-strand breaks with other kinds of DNA damage nearby—such complex breaks are more relevant physiologically, Dr. Daley said. Studies in the field of DNA repair usually tend to look at simpler versions of double-strand breaks, he said. Dr. Daley found that each resection enzyme is tailored to deal with a specific type of complex break, which explains why a diverse toolkit of resection enzymes has evolved over millennia.

Cancer ramifications

Dr. Burma, the Mays Family Foundation Distinguished Chair in Oncology at UT Health San Antonio MD Anderson Cancer Center, said the fundamental understandings gleaned from this research could one day lead to improved cancer treatments.

"The cancer therapeutic implications are immense," Dr. Burma said. "This research by our team is timely because a new type of radiation therapy, called carbon ion therapy, is now being considered in the U.S. While being much more precisely aimed at tumors, this therapy is likely to induce exactly the sort of complex DNA damage that we studied. Understanding how specific enzymes repair complex damage could lead to strategies to dramatically increase the efficacy of cancer therapy."

Part of the research is funded by NASA. "These kinds of complex DNA breaks are also induced by space radiation," Dr. Burma said. "Therefore, the research is relevant not just to cancer therapy, but also to cancer risks inherent to space exploration."

More information: James M. Daley et al, Specificity of end resection pathways for double-strand break regions containing ribonucleotides and

base lesions, *Nature Communications* (2020). DOI: 10.1038/s41467-020-16903-4

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