Researchers discover how enzyme protects cells from DNA damage

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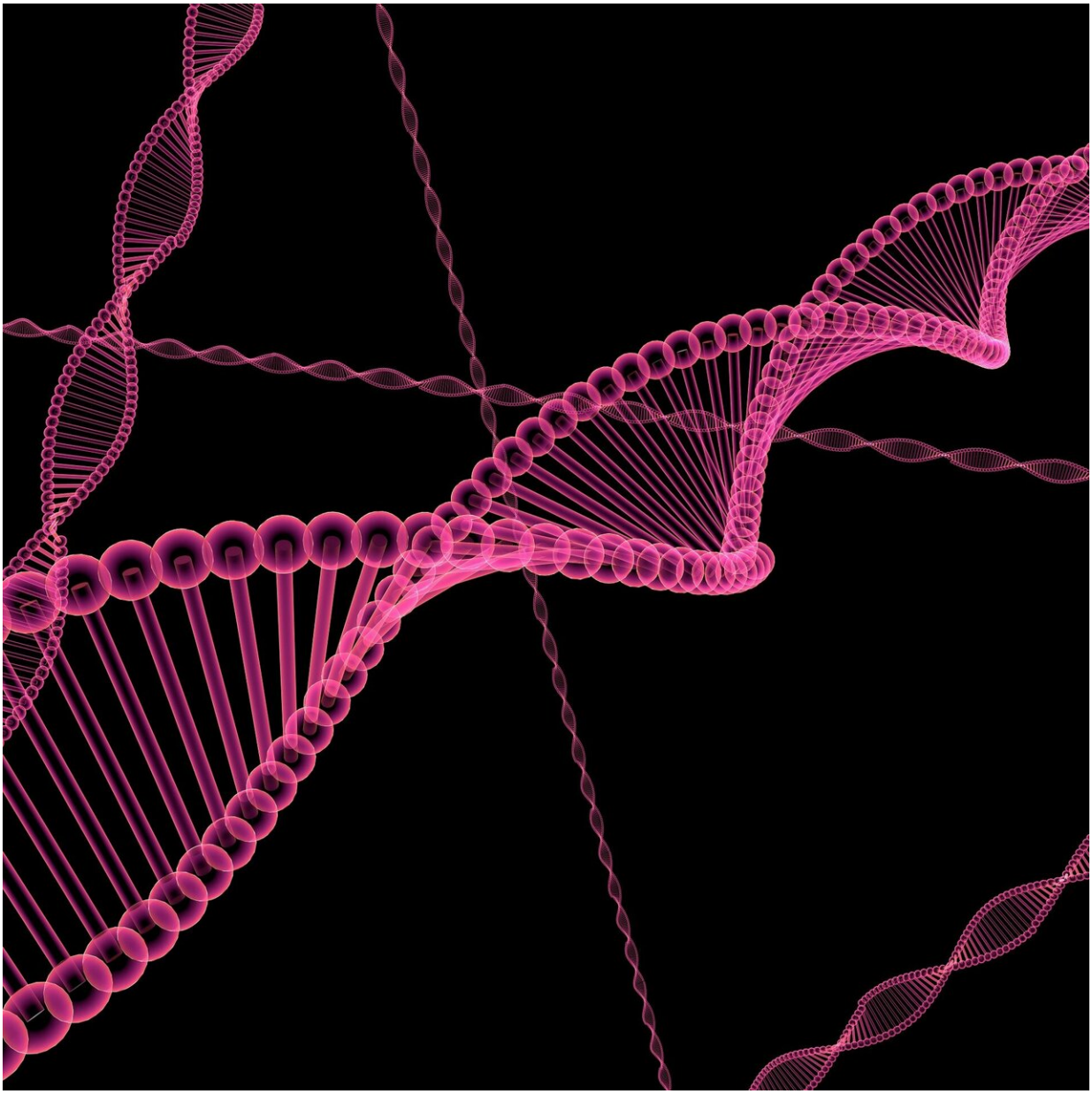

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A research team from Mount Sinai has unraveled for the first time the three-dimensional structure and mechanism of a complex enzyme that protects cells from constant DNA damage, opening the door to discovery of new therapeutics for the treatment of chemotherapy-resistant cancers. In a study published in *Nature Structural & Molecular Biology* in August, the researchers described how they used advanced cryo-electron microscopy to gain detailed insights into the enzyme known as DNA polymerase ζ (Pol ζ), whose architecture and mechanism have been a mystery to scientists for years.

"Resolving the structure of the complete Pol ζ enzyme at near-atomic resolution allows us to address long-standing questions of how this unique polymerase replicates through daily DNA-damaging events, while also providing a template for designing drugs against cancers that are refractory to conventional chemotherapeutics," says lead author Aneel Aggarwal, Ph.D., Professor of Pharmacological Sciences at the Icahn School of Medicine at Mount Sinai.

DNA polymerase ζ is the crucial enzyme that allows cells to battle the more than 100,000 DNA-damaging events that occur daily from normal metabolic activities and environmental intrusions like ultraviolet light, ionizing radiation, and industrial carcinogens. The Mount Sinai team, which included first author Radhika Malik, Ph.D., Assistant Professor of Pharmacological Sciences, learned how the enzyme protects the cells from natural and manmade environmental as well cellular stresses through an intricate structure of four different proteins that connect to each other in a pentameric, or daisy chain-like, configuration.

This architecture is expected to provide valuable insights to scientists for

the future development of drugs designed to inhibit the DNA polymerase when treating cancers like non-small-cell lung, prostate, and ovarian that often become resistant to chemotherapy after early use in patients. The reason for that resistance is that chemotherapies like cisplatin actually depend on their DNA-damaging effects. Thus, blocking or inhibiting the function of Pol ζ makes the cancerous cells more sensitive to the therapeutic impact of chemotherapy.

"The development of effective inhibitors has been hampered in the past by a lack of structural information on Pol ζ," explains Dr. Aggarwal. "Our work now offers a much clearer picture, and we expect these new insights will spur efforts by scientists around the world to create effective new therapies. For the thousands of patients with tumors that are resistant to chemotherapy, these findings could prove to be particularly valuable by meeting an unfulfilled need in their battle against cancer."

The lack of progress over the years was largely due to the fact that structural studies of DNA polymerase ζ were limited by the low yields and unattainability of well-diffracting crystals. Dr. Aggarwal and his team overcame that problem by employing cryo-electron microscopy. This technology, which allows for the imaging of rapidly frozen molecules in solution, is revolutionizing the entire field of structural biology through its high-resolution pictures of complex molecules.

More information: Structure and mechanism of B-family DNA polymerase ζ specialized for translesion DNA synthesis, *Nature Structural & Molecular Biology* (2020). DOI: 10.1038/s41594-020-0476-7 , www.nature.com/articles/s41594-020-0476-7

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