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Researchers provide molecular portraits of a new cancer drug target

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Unprecedented images of cancer genome-mutating enzymes acting on DNA provide vital clues into how the enzymes work to promote tumor evolution and drive poor disease outcomes. These images, revealed by University of Minnesota researchers, provide the first ever high-resolution pictures of molecular complexes formed between DNA and the human APOBEC3A and APOBEC3B enzymes.

The research is published today online in *Nature Structural and Molecular Biology*.

The DNA mutating enzymes called APOBECs are a major source of mutation in breast, lung, cervical, head/neck and many other cancer types.

"These enzymes normally function to protect us from viral infections," said Reuben Harris, Ph.D., investigator of the Howard Hughes Medical Institute and professor of Biochemistry, Molecular Biology, and Biophysics, member of the Masonic Cancer Center, and associate director of the Institute of Molecular Virology, University of Minnesota. "However, these enzymes can become misregulated in cancer cells and cause mutations in our own genomic DNA. These mutations fuel tumor evolution and promote poor clinical outcomes such as drug resistance and metastasis."

With an imaging technique called x-ray crystallography, which uses a high energy x-ray beam to visualize the atomic details of molecules,

researchers were able to see an unexpected mode of DNA binding activity. A unique U-shaped DNA conformation and defined pockets for the target cytosine and the adjacent thymine base explains the specific mutation signature left behind by the enzyme interacting with tumor DNA.

"Our crystal structures and corroborating biochemical experiments show how APOBEC3A and APOBEC3B engage DNA substrates," said Hideki Aihara, Ph.D., associate professor in the department of Biochemistry, Molecular Biology and Biophysics and member of the Institute of Molecular Virology and the Masonic Cancer Center at the University of Minnesota. "These structures show an unexpected mode of DNA engagement with a sharply bent DNA strand and flipped-out nucleotides. Our findings were surprising, but actually make a lot of sense and explain many previous observations about this family of proteins."

The DNA-binding mechanism suggests ways to block enzyme activity in cancer, which could slow the rate at which tumors evolve. Inhibiting APOBEC activity could make current anti-cancer therapies more effective.

Work continues to take and analyze additional portraits of these enzymes with different DNA substrates and to devise strategies for enzyme inhibition.

More information: Structural basis for targeted DNA cytosine deamination and mutagenesis by APOBEC3A and APOBEC3B, *Nature Structural and Molecular Biology*, nature.com/articles/doi:10.1038/nsmb.3344