Research team discovers role of key enzymes that drive cancer mutations

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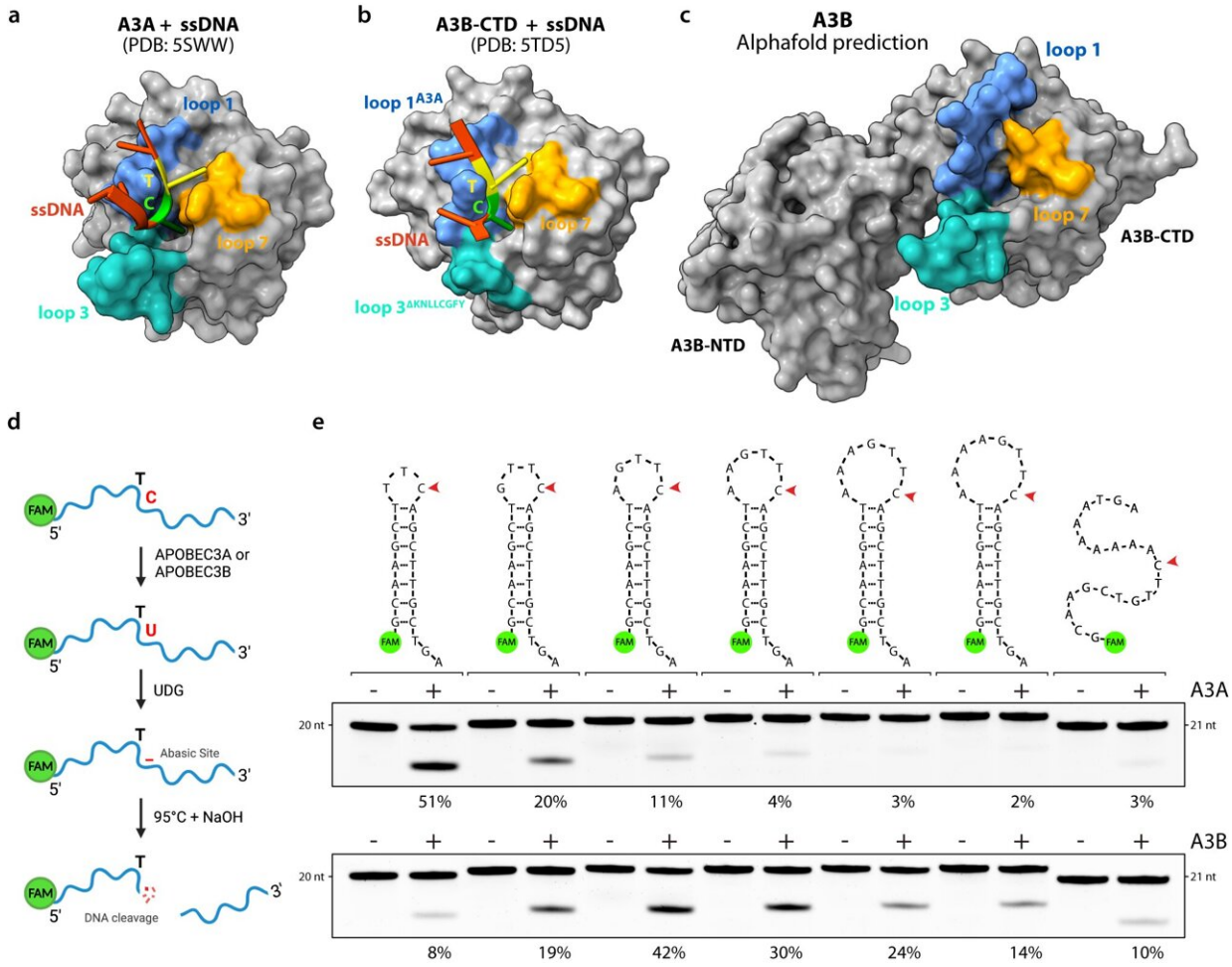

APOBEC3A and APOBEC3B preferentially target U-shaped DNA. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45909-5

A research team led by the University of California, Irvine has discovered the key role that the APOBEC3A and APOBEC3B enzymes play in driving cancer mutations by modifying the DNA in tumor genomes, offering potential new targets for intervention strategies.

The study, published online in the journal *Nature Communications*, describes how the researchers identified the process by which APOBEC3A and APOBEC3B detect specific DNA structures, resulting in mutations at distinct positions within the tumor genome.

"It's critical to understand how cancer cells accumulate mutations leading to hot spots that contribute to disease progression, drug resistance and metastasis," said corresponding author Rémi Buisson, UCI assistant professor of biological chemistry.

"Both APOBEC3A and APOBEC3B were known to generate mutations in many kinds of tumors, but until now we did not know how to identify the specific type caused by each. This finding will allow us to develop novel therapies to suppress mutation formation by directly targeting each enzyme accordingly."

In this study, graduate student Ambrocio Sanchez and postdoctoral fellow Pedro Ortega, both in Buisson's laboratory at the UCI School of Medicine, developed a new method to characterize the particular kind of DNA modified by APOBEC3A and APOBEC3B.

It revealed that the two enzymes do not recognize the same DNA sequences and structures within the genomes of cancer cells. Based on this observation, an innovative approach utilizing these unique target preferences was employed to classify cancer patients who had accumulated mutations caused by each enzyme.

"The next steps are to investigate whether mutations caused by these

enzymes lead to various types of therapy resistance. It's also critical to identify molecules that inhibit APOBEC3A and APOBEC3B to prevent mutations from forming. Our findings could, in the future, help to assess patient risk before treatment and suppress tumor evolution using the appropriate drug therapy," Buisson said.

Other team members included undergraduate and graduate students and postdoctoral fellows from UCI, Harvard Medical School, the University of Southern California, the University of Texas at San Antonio and the University of Minnesota.

More information: Ambrocio Sanchez et al, Mesoscale DNA features impact APOBEC3A and APOBEC3B deaminase activity and shape tumor mutational landscapes, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45909-5

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