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Researchers uncover a novel protein which drives cancer progression

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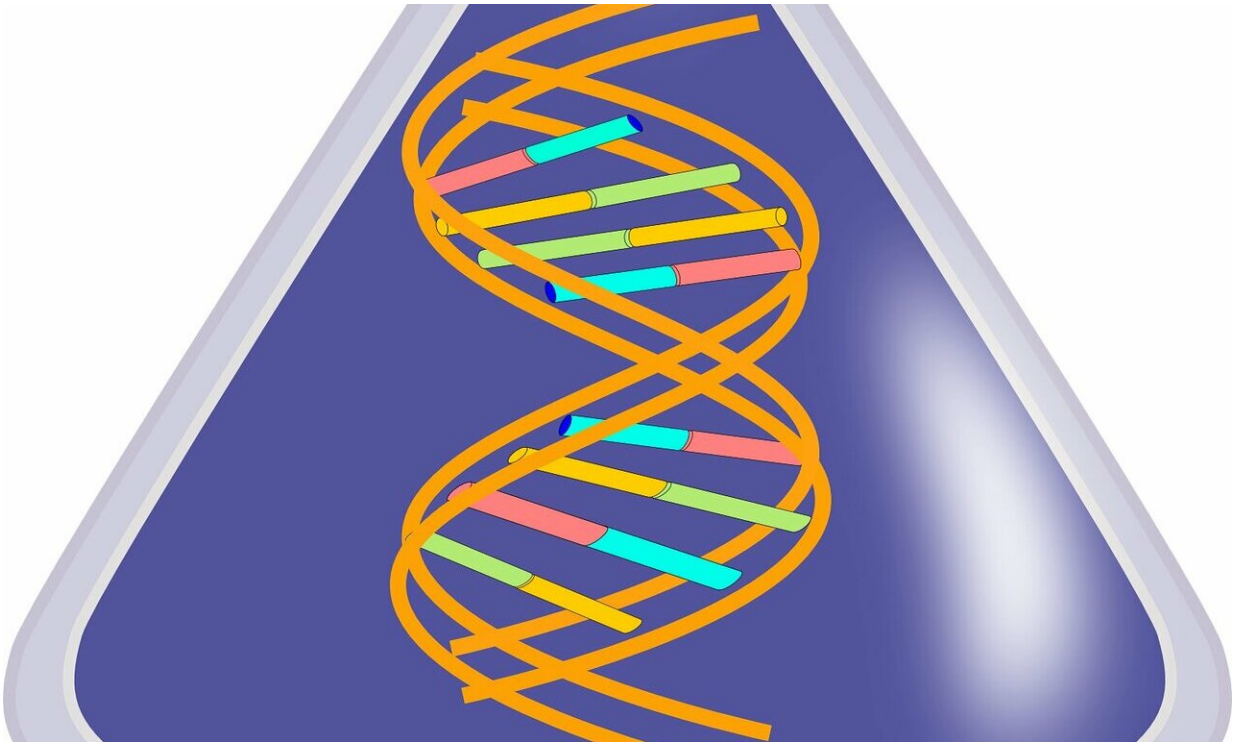

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Cancers arise when the genetic code of normal cells is altered, causing excessive growth. Researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) have discovered a protein that drives the growth of cancers of the esophagus or liver by altering the genetic code in a novel way.

The protein, death associated protein 3 (DAP3), represses a process called adenosine-to-inosine (A-to-I) RNA editing that normally corrects the genetic code to ensure that genes are expressed correctly. By inhibiting RNA editing, DAP3 acts as an oncogene—a gene that has the potential to cause cancer. This discovery offers the potential of developing novel drugs that target DAP3 for cancer treatment.

The study was led by Assistant Professor Polly Chen, a Principal Investigator at CSI Singapore, and the findings were published in the scientific journal *Science Advances* on 17 June 2020.

Understanding A-to-I RNA editing

RNAs are one of the most important classes of molecules in cells. They not only convert the genetic information stored in DNA to proteins, but also play critical regulatory roles in various biological processes. RNA editing is a process in which RNA is changed after it is made from DNA, resulting in an altered gene product. In humans, the most common type of RNA editing is A-to-I editing, which is mediated by ADAR proteins (ADAR1 and ADAR2). In the past decade, many studies have reported that the accumulation of deleterious changes in A-to-I RNA editing can trigger a cell to develop into cancer. However, the current knowledge of how the A-to-I RNA editing process is regulated in cancer is still limited.

The CSI Singapore research team therefore conducted a research study to understand how DAP3—the interacting protein of the A-to-I RNA editing catalytic enzymes (ADAR1 and ADAR2)—regulates this process in cancer cells.

Promising drug target for cancer treatment

The team demonstrated that DAP3 could destroy the binding of ADAR2 protein to its target RNAs, thereby inhibiting the A-to-I RNA editing in cancer cells. This suppression is likely to be one of the pathways by which DAP3 could promote cancer development.

Their analysis also revealed that the expression of DAP3 is elevated in 17 types of cancer. Further experiments demonstrated that DAP3 acted as an oncogene in esophageal cancer and liver cancer cells. Interestingly, they also identified the gene PDZD7, one of DAP3-inhibited editing targets and discovered that altered editing of PDZD7 generated a new PDZD7 protein product which contributed to the DAP3-driven tumor growth.

Overall, these observations shed light on the complexity of the regulation of the A-to-I RNA editing process in cancer cells, and suggest that DAP3 could be a promising target for future cancer drug development.

"With this new knowledge, we can now look into how we can intervene in the interactions between DAP3 and ADAR proteins in order to interfere with cancer-promoting processes mediated by RNA editing in the cell," said research leader Asst Prof Chen.

More information: Jian Han et al, Suppression of adenosine-to-inosine (A-to-I) RNA editome by death associated protein 3 (DAP3) promotes cancer progression, *Science Advances* (2020). DOI: 10.1126/sciadv.aba5136

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