Researchers discover cancer hijacks a class of enzyme motif mutations to fuel tumorigenesis

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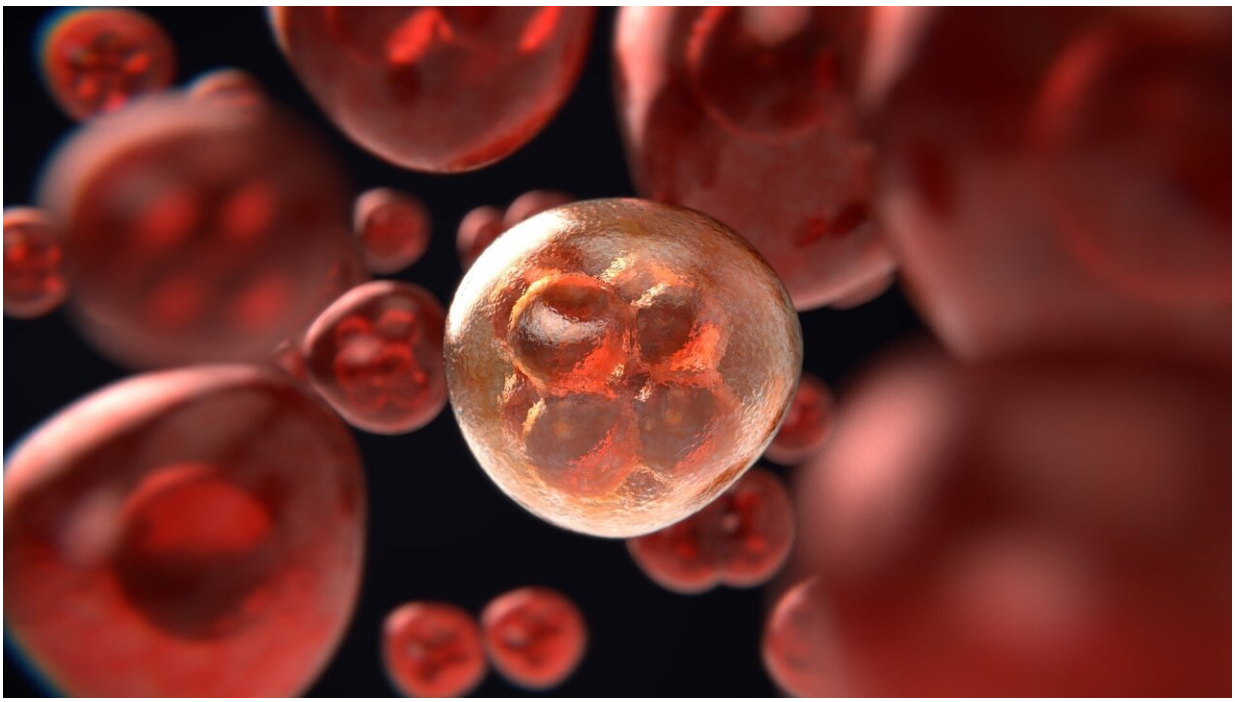

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Cancer spreads throughout the human body in cunning, almost militaristic, ways. For example, it can manipulate our genetic make-up, take over specific cell-to-cell signaling processes, and mutate key enzymes to promote tumor growth, resist therapies, and hasten its spread

from the original site to the bloodstream or other organs.

Enzyme mutations have been of great interest to scientists who study cancer. Scientists in the Liu and Tan labs at UNC's Lineberger Comprehensive Cancer Center have been studying mutations of enzyme recognition motifs in substrates, which may more faithfully reflect enzyme function with the potential to find new targets or directions for cancer treatment.

"We think understanding the roles of mutations on enzyme substrates, instead of the enzyme as a whole, may help to improve efficacy of targeted therapies, especially for enzymes that have both oncogenic and tumor suppressive function through controlling distinct subsets of substrates," said Jianfeng Chen, Ph.D., who is first author and a postdoctoral fellow in the Liu lab in the UNC Department of Biochemistry and Biophysics.

Their results were published in *Journal of Experimental Medicine* on June 29, 2023.

AGC kinase motif mutations

Using the developed algorithm and information from The Cancer Genome Atlas (TCGA), the researchers found that the highest rate of mutation occurs in the AGC kinase motif called RxRxxS/T. RxRxxS/T is a short, recurring pattern that is shared among the AGC family of ~60 kinases. These enzymes play critical roles in metastasis, proliferation, drug resistance, and development.

"We found that cancer tried to either evade or create mutations on these RxRxxS/T motifs to give itself more advantages for tumor growth and survival," said Pengda Liu, Ph.D., who is an associate professor of biochemistry and biophysics.

A new mechanism for colorectal cancer

The Liu and Tan groups conducted a validation study on the AGC kinase motif mutations associated with colorectal cancer, the second most lethal cancer and the third most prevalent malignant tumor worldwide. Currently, colorectal cancer has a 5-year survival rate of 12%.

They discovered that colon cancer "hijacks" BUD13 mutations, a protein-coding gene, to sidestep the phosphorylation that are carried out by AGC kinase. Colon cancer ultimately prefers these BUD13 mutations because it gains an additional benefit by inactivating an E3 ligase called Fbw7. "Turning off" Fbw7, a crucial tumor suppressor, causes an increase in tumor growth and therapy resistance.

In addition to their findings on Fbw7 inactivation, the research team also found that the BUD13 tumor cells were more susceptible to the inhibition of mTORC2 kinase, revealing a new, potential targeted therapy for colon cancer patients bearing that have the BUD13 mutation.

"It is exciting to teasing out different types of somatic mutations and we are glad to offer this publicly available resources to cancer research community," said Xianming Tan, Ph.D., who is a research associate professor in the Department of Biostatistics in the Gillings School of Public Health and the Lineberger Comprehensive Cancer Center.

To search for protein motif mutations in the TCGA database, click here.

More information: Jianfeng Chen et al, Somatic gain-of-function mutations in BUD13 promote oncogenesis by disrupting Fbw7 function, *Journal of Experimental Medicine* (2023). DOI: 10.1084/jem.20222056