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Scientists find new drug targets in aggressive cancers

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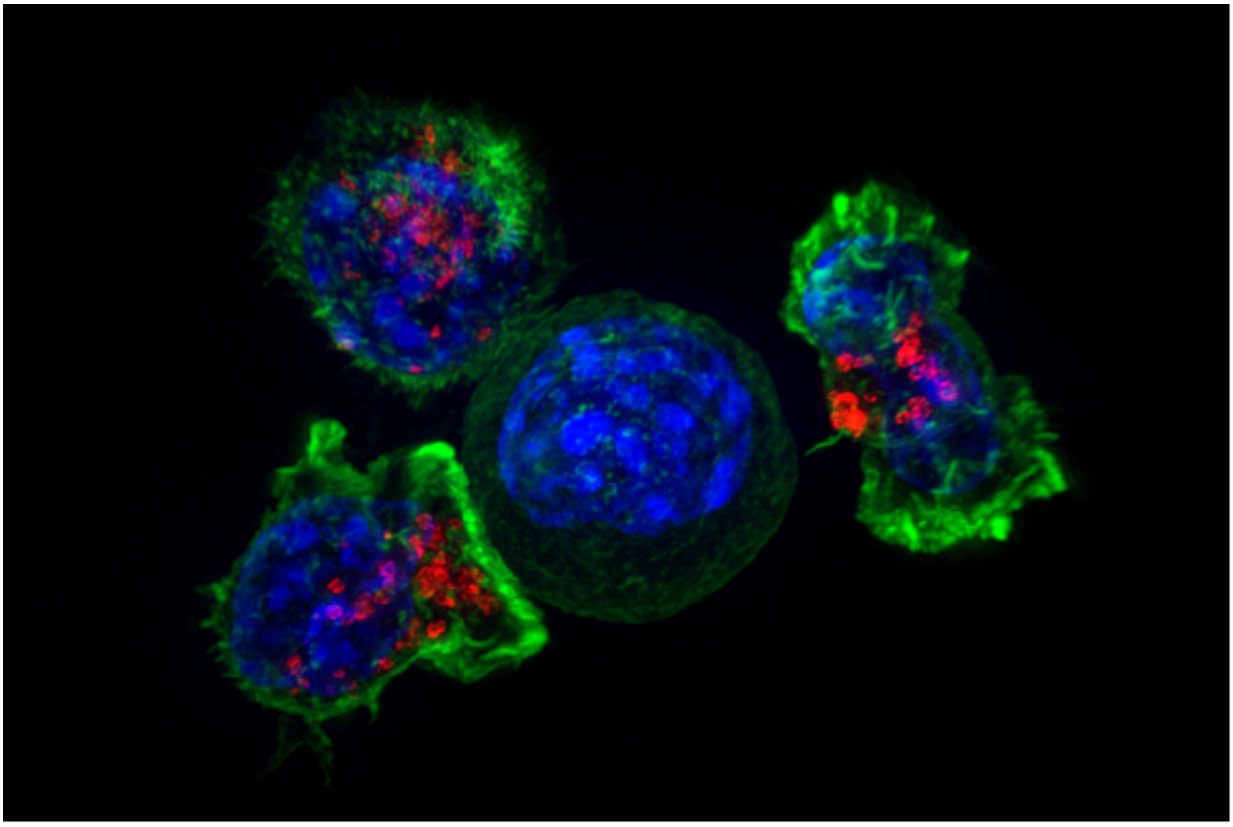

Killer T cells surround a cancer cell. Credit: NIH

Scientists have discovered a previously unknown molecular vulnerability in two rare, aggressive, and hard-to-treat types of cancer, and say it may be possible to attack this weakness with targeted drugs.

Reporting in *Nature Cell Biology*, researchers at Dana-Farber Cancer Institute show that these two cancers—synovial sarcoma and malignant rhabdoid tumors—are dependent on a newly characterized "molecular machine" called ncBAF, which plays unique roles in regulating gene activity. The scientists showed that biologically and chemically disabling components of ncBAF—which is made up of several unique protein subunits—specifically impaired the proliferation of two types of cancer cell lines which share a common disruption.

"This is one of the first suggestions toward a route for therapeutic intervention in these intractable, aggressive cancers," said Cigall Kadoch, Ph.D., of Dana-Farber Cancer Institute, senior author of the report in *Nature Cell Biology*. "These findings identify new, cancer-specific targets which may be extendable to other cancer types as well."

Synovial sarcoma is a rare cancer of soft tissues that typically is diagnosed in young adults. Malignant rhabdoid tumors are also rare but are very aggressive and usually develop in children under the age of two. They can affect the brain, kidney, and other organs.

Recent work by Kadoch's team as well as other groups has implicated these molecular machines, called chromatin-remodeling complexes, in the development and maintenance of cancer. These complexes are clusters of proteins that remodel the way the DNA in a cell is packaged—and in doing so, help regulate which genes are turned on and off. Each of the complexes is made up of numerous protein subunits.

Kadoch's research has focused on a category of chromatin remodeling complexes known as the SWI/SNF family. There are three types of complexes in the family—cBAF, PBAF, and ncBAF. Two weeks ago, in Cell, the Kadoch group reported the order of assembly and modular organization of these complexes for the first time. Importantly, these chromatin remodelers travel to various locations on the DNA genome

within the cell and regulate which genes are turned on, and when, to generate the cell's proteins needed at various times. It's estimated that 20 percent of human cancers are associated with mutations in the genes that code for the chromatin-remodeling complex subunits, resulting in disruption of gene expression and leading to the development of tumors.

In the current study, the researchers report that the ncBAF complex (nc stands for non-canonical) differs from the other two complexes (cBAF and PBAF) in several ways, including where on the genome it acts. In addition, ncBAF is different because it contains two subunits, BRD9 and GLTSCR1, that aren't parts of any other complexes, and lacks subunits that are found in other complexes.

Most intriguingly—and relevant for cancer—the researchers found that ncBAF function is specifically required by synovial sarcoma and malignant rhabdoid tumors to maintain their cell division and growth. Owing to its dependence in these cancers, ncBAF is termed a "synthetic lethal target," suggesting that disrupting ncBAF could be a viable approach to treating these tumors.

Kadoch and her colleagues are particularly interested in the BRD9 subunit of the ncBAF complex, because there are existing small molecule probes that can block BRD9 activity, as well as experimental agents, known as protein degraders, that are designed to eliminate BRD9 from cells.

"This was an unexpected target, and these findings are already being explored pre-clinically" in hopes of treating the two rare cancers, Kadoch says. Co-first authors of the work are Brittany Michel, Andrew D'Avino, and Seth Cassel.

More information: A non-canonical SWI/SNF complex is a synthetic lethal target in cancers driven by BAF complex perturbation, *Nature Cell*

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