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Protein complex may play role in preventing many forms of cancer, study shows

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Researchers at the Stanford University School of Medicine have identified a group of proteins that are mutated in about one-fifth of all human cancers. The finding suggests that the proteins, which are members of a protein complex that affects how DNA is packaged in cells, work to suppress the development of tumors in many types of tissues.

The broad reach of the effect of mutations in the complex, called BAF, rivals that of another well-known tumor suppressor called p53. It also furthers a growing notion that these so-called chromatin-regulatory complexes may function as much more than mere cellular housekeepers.

"Although we knew that this complex was likely to play a role in preventing cancer, we didn't realize how extensive it would be," said postdoctoral scholar Cigall Kadoch, PhD. "It's often been thought that these complexes play supportive, maintenance-like roles in the cell. But this is really changing now."

Kadoch shares lead authorship of the study with postdoctoral scholar Diana Hargreaves, PhD. Gerald Crabtree, MD, professor of developmental biology and of pathology, is the senior author of the study, which will be published online May 5 in *Nature Genetics*.

Chromatin-regulatory complexes work to keep DNA tightly condensed, while also granting temporary access to certain portions for replication or to allow the expression of genes necessary for the growth or function

of the cell.

Members of Crabtree's laboratory have been interested in BAF complexes and their function for many years. Recently, they reported in the journal *Nature* that switching subunits within these complexes can convert human fibroblasts to neurons, which points to their instructive role in development and, possibly, cancer.

"Somehow these chromatin-regulatory complexes manage to compress nearly two yards of DNA into a nucleus about one one-thousandth the size of a pinhead," said Crabtree, who is also a member of the Stanford Cancer Institute and a Howard Hughes Medical Institute investigator. "And they do this without compromising the ability of the DNA to be replicated and selectively expressed in different tissues - all without tangling. In 1994 we reported that complexes of this type were likely to be tumor suppressors. Here we show that they are mutated in nearly 20 percent of all human malignancies thus far examined."

The researchers combined biochemical experiments with the data mining of 44 pre-existing studies to come to their conclusions, which would not have been possible without the advent of highly accurate, genome-wide DNA sequencing of individual human tumor samples. Interestingly, mutations to certain subunits, or particular combinations of mutations in the complex's many subunits, seem to herald the development of specific types of cancer - favoring the development of ovarian versus colon cancer, for example.

The importance of the BAF complex as a tumor suppressor is further emphasized by the fact that, in some cases, a mutation in one subunit is sufficient to initiate cancer development.

"For example," said Kadoch, "a type of mutation called a chromosomal translocation in the gene encoding one of these newly identified

subunits, SS18, is known to be the hallmark of a cancer called synovial sarcoma. It is clearly the driving oncogenic event and very often the sole genomic abnormality in these cancers." Kadoch and Crabtree published a study in March in *Cell* uncovering the mechanism and functional consequences of BAF complex perturbation in synovial sarcoma.

The startling prevalence of mutations in the BAF complex was discovered when Kadoch conducted a series of experiments to determine exactly which proteins in the cell were true subunits of the complex. (The exact protein composition of the large complex varies among cell types and species.) Kadoch used an antibody that recognized one core component to purify intact BAF complexes in various cell types, including embryonic stem cells and skin, nerve and other cells. She then analyzed the various proteins isolated by the technique.

Using this method, Kadoch identified seven proteins previously unknown to be BAF components. She and Hargreaves then turned to previously published studies in which the DNA from a variety of human tumors had been sequenced to determine how frequently any of the members of the complex were mutated.

The results, once the newly discovered members were included, were surprising: 19.6 percent of all human tumors displayed a mutation in at least one of the complex's subunits. In addition, for some types of cancers (such as synovial sarcoma), every individual tumor sample examined had a mutation in a BAF subunit. The results suggest that the BAF complex, when unmutated, plays an important protective role against the development of cancer in many different tissues.

The researchers are now focused on learning how the mutations affect the tumor-suppressing activity of the BAF complex.

"We certainly want to further our understanding of the mechanism

behind these findings," said Hargreaves. "Do they promote cancer development by inhibiting the proper progression of the cell cycle? Or perhaps they affect how the complex is positioned on the DNA. We'd like to determine how to recapitulate some of these mutations experimentally to see what types of defects they introduce into the complex."

More information: Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy, DOI: 10.1038/ng.2628

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