

Researchers Identify Key Molecular Event Leading to Synovial Sarcoma

The findings also help explain why a class of targeted drugs don't appear to be effective for this rare cancer that occurs in adolescents and young adults.

August 27, 2018 By Megan Riesz

Cancer biologists led by Cigall Kadoch, PhD, of [Dana-Farber Cancer Institute](#), have identified a key molecular event that leads to [synovial sarcoma](#), a rare, aggressive cancer in adolescents and young adults for which scientists are seeking better treatments.

The researchers, whose work was published in *Cancer Cell*, say that a mutant protein known as a fusion oncoprotein “hijacks” groups of proteins known as BAF complexes which reside on chromatin (the structure of DNA wrapped around histones in the nucleus). It achieves this by shifting these BAF complexes to different locations in the genome, where they activate cancer-promoting genes that lead to the growth of synovial sarcoma tumors.

BAF complexes perform critical “chromatin remodeling” tasks—that is, determining which segments of the DNA blueprint in a cell will be converted into proteins that carry out the cell's function.

The findings not only shed new light on the gene regulatory malfunctions that occur in the sarcoma, but also help explain why a class of targeted drugs known as EZH2 inhibitors that are being tested in clinical trials appear not to be effective for this form of cancer.

“The study shows that understanding the structure and function of this intricate complex is critical to properly informing therapeutic approaches,” says Kadoch.

Synovial sarcoma is uniformly driven by the SS18-SSX fusion oncoprotein that results from a genetic change called a chromosomal translocation. This cancer-causing event is the hallmark of every case of the rare cancer.

The normal, healthy job of BAF complexes is to orchestrate the turning on and off of multiple genes involved in appropriate cellular function—for example, during human development, where an embryo needs to differentiate into many highly specialized tissues. Kadoch has previously found that more than 20 percent of human cancers involve mutations in the genes that code for BAF complexes. BAF gene mutations may also be implicated in syndromes causing intellectual

disabilities.

It was previously known that the fundamental culprit in synovial sarcoma is the formation of an abnormal fusion protein, SS18-SSX, from two broken pieces of a chromosome. Several years ago, Kadoch discovered that this fusion protein inserts itself into the regulatory BAF complex—which comprises a number of proteins – and changes its composition. Specifically, a nearby component called BAF47 is dislodged from the complex.

In their new report, Kadoch and colleagues demonstrate that it is the dominant role of SS18-SSX, and not the secondary dislodging of any other subunits in the complex such as BAF47, that drives synovial sarcoma. This is important in that it presents a mechanistic reason why EZH2 inhibitors which target polycomb repressive complexes, and which are used in cancers driven by faulty BAF complexes (such as malignant rhabdoid tumors and epithelioid sarcomas which exhibit loss of BAF47), are thus far not showing clinical efficacy in synovial sarcoma.

“We find that the SS18-SSX fusion protein hijacks BAF complexes away from their normal sites on the genome to new sites at which they oppose repressive complexes and activate oncogenic, synovial sarcoma-specific gene expression and proliferation,” explains Kadoch. “This is an important advance suggesting that mistargeting of a major chromatin regulator underpins the action of the SS18-SSX fusion protein, and implicates the specific interface between the SS18-SSX-bound BAF complex and chromatin as a potential therapeutic target.”

First authors of the study are Matthew McBride and John Pulice, graduate students in the Kadoch laboratory.

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