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Team defines the mechanisms of action of key genetic abnormality in Ewing sarcoma

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A Massachusetts General Hospital (MGH) research team has used epigenome editing tools to investigate how the genetic abnormality that drives Ewing sarcoma—the second most common bone cancer in children and young adults—unleashes tumor growth. In their paper in the journal *Genes & Development* the researchers show that blocking the fusion protein EWS-FLI1 from binding and activating specific 'enhancer' sites in the genome prevents the expression of genes that promote tumor growth.

"We previously showed that binding of EWS-FLI1 to GGAA microsatellite repeats in the genome converts these sites into active enhancers," says Miguel Rivera, MD, MGH Department of Pathology and Center for Cancer Research, co-senior author of the report. "Now we have used new epigenome editing tools to turn off individual microsatellites and demonstrate that they have important functions in controlling the expression of nearby genes that are critical for tumor growth."

Ewing sarcoma is caused by a genetic alteration known as a chromosomal translocation in which the chromosome 22 gene EWS is fused to the chromosome 11 gene FLI1, leading to generation of the fusion protein EWS-FLI1. A 2014 *Cancer Cell* study led by Rivera and Bradley Bernstein, MD, Ph.D., also of MGH Pathology and the Center for Cancer Research, found that EWS-FLI1 had two properties that could lead to tumor growth: conversion of microsatellite repeats—repetitive DNA elements commonly found in the

genome—into active enhancers that stimulate the expression of other genes and repression of other factors that regulate gene transcription. In essence, EWS-FLI1 both steps on the gas and takes off the brakes to tumor growth.

The current study was designed to directly test the links between microsatellite activation by EWS-FLI1, the expression of cancer-associated genes and tumor growth. The researchers focused on GGAA microsatellites—repeats of the nucleotides guanine and adenine—that are usually inactive but in Ewing sarcoma are bound and activated by EWS-FLI1.

The investigators used a novel CRISPR-based system to bring a repressor module to sites adjacent to the GGAA microsatellites in Ewing sarcoma cells, which markedly reduced expression of nearby genes believed to stimulate tumor growth. In contrast, repression of GGAA repeats in cancer cells that did not express the fusion protein had no effect on gene expression. Finally, silencing a specific repeat known to regulate expression of SOX2, a transcription factor that acts as an oncogene, led to a significant decrease in the size of Ewing sarcoma tumors in mice.

"Finding regulatory regions such as enhancers in the genome that are specifically utilized in tumors but not in normal cells may point to new therapeutic opportunities," says Rivera, an assistant professor of Pathology at Harvard Medical School. "We're now working towards identifying other tumor-specific enhancers that are important for tumor growth in Ewing sarcoma and other types of cancer."

More information: Gaylor Boulay et al, Epigenome editing of microsatellite repeats defines tumor-specific enhancer functions and dependencies, *Genes & Development* (2018). DOI: 10.1101/gad.315192.118

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