Single genetic abnormality accelerates, removes the brakes on Ewing sarcoma tumor growth

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The genetic abnormality that drives the bone cancer Ewing sarcoma operates through two distinct processes - both activating genes that stimulate tumor growth and suppressing those that should keep cancer from developing. These findings by Massachusetts General Hospital (MGH) investigators, published in the November issue of *Cancer Cell*, may lead to new therapies targeting these aberrant mechanisms.

The second most common bone cancer in children and young adults, Ewing sarcoma is caused by a chromosomal translocation - switching of genetic segments between two different chromosomes - in which the chromosome 22 gene EWS is fused to the chromosome 11 gene FLI1. Exactly how that abnormality, which produces a fusion protein called EWS-FLI1, leads to tumor development was not known, although it had been recognized that FLI1 and related proteins were transcription factors that regulate the expression of other genes.

Led by Miguel Rivera, MD, and Bradley Bernstein, MD, PhD, of the MGH Department of Pathology and Center for Cancer Research, the investigators analyzed how regulatory changes resulting from the EWS-FLI1 fusion alter the activation and repression of regions across the genome. This approach, called chromatin profiling, is a powerful tool for determining how transcription factors act in cancer and revealed that EWS-FLI1 acts through two different mechanisms.

First the fusion protein converts common repetitive elements within the genome into active enhancing elements that stimulate the expression of other genes. This 'pioneer' function is remarkable, Rivera notes, because while these repeat segments have no known function outside the setting of Ewing sarcoma, they are critical for the development of the tumor. The second property of the EWS-FLI1 fusion is to turn off factors that regulate gene transcription at a different group of sites. In essence the abnormal protein both stimulates the abnormal cellular growth that leads to tumor formation and turns off factors that should keep that growth in check.

"Uncovering the molecular functions of EWS-FLI1 points to processes that may be targeted therapeutically" says Rivera, an assistant professor of Pathology at Harvard Medical School. "In addition, some of the genes directly turned on by EWS-FLI1 may themselves be therapeutic targets. One such gene, the kinase VRK1, is regulated by an EWS-FLI1-dependent enhancer that is active in Ewing sarcoma cell lines, and we found that its expression is essential for the survival of Ewing sarcoma cells. These studies also underscore the importance of performing epigenetic analysis to understand the biological pathways that are altered in cancer."

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