Published OnlineFirst December 14, 2018; DOI: 10.1158/2159-8290.CD-RW2018-212

Transcription

Major finding: ZFP64 binds to the *MLL* promoter and is essential for the growth of *MLL*-rearranged leukemia cells.

Concept: The *MLL* promoter has a high density of ZFP64 binding sites and is the most enriched locus for ZFP64 occupancy.

Impact: Binding motif density in oncogene promoters may be linked to transcriptional vulnerabilities in cancer.

TRANSCRIPTION FACTOR MOTIF DENSITY CAN CONFER TRANSCRIPTIONAL ADDICTION

MLL translocations occur in approximately 5% of acute myeloid and lymphoid leukemias and are associated with a poor prognosis. MLL rearrangements corrupt the transcriptional function of the MLL protein, prompting Lu and colleagues to conduct a domain-focused CRISPR screen of transcription factor DNA-binding domains to identify transcription factor vulnerabilities in a panel of human cancer cell lines, including four MLL-rearranged leukemia cell lines. Zinc finger protein 64 (ZFP64) scored as one of the top transcription factors that was specifically essential in the *MLL*-rearranged and *MLL*-addicted leukemia cell lines compared with *MLL*–wild-type cell lines. Chromatin immunoprecipitation followed by DNA sequencing and *de novo* motif discovery analysis allowed the identification of a 15-nucleotide sequence motif that correlated with ZFP64 occupancy and suggested that ZFP64 acts as a transcriptional activator based on the overlap of ZFP64 binding sites with active chromatin marks. Unexpectedly, ZFP64 did not colocalize with MLL at genomic loci or physically interact with MLL; instead, the gene encoding MLL was identified as a direct ZFP64 target gene and the *MLL* promoter was the most highly enriched site of ZFP64 occupancy in both the human and mouse genomes. This was likely attributable to the exceptionally high density of ZFP64 binding motifs in the *MLL* promoter compared with other intervals in the genome. ZFP64 binding at the MLL promoter was required for activation of MLL expression and constituted the essential function of ZFP64 in leukemia cells. As outlier transcription factor binding motif densities can be found in the promoters of many human genes, including oncogenes, these findings represent proof-of-principle that high binding motif densities may confer transcriptional vulnerabilities and raise the possibility that this may be a common mechanism of transcriptional addiction in cancer. ■

Lu B, Klingbeil O, Tarumoto Y, Somerville TDD, Huang YH, Wei Y, et al. A transcription factor addiction in leukemia imposed by the MLL promoter sequence. Cancer Cell 2018;34:970–81.

Breast Cancer

Major finding: Loss of the tumor suppressors *FAT1* or *RB1* promotes CDK4/6 inhibitor resistance in ER$^+$ breast cancer.

Mechanism: The *FAT1* loss–mediated nuclear localization of YAP promotes CDK6 expression.

Impact: Hippo pathway alterations may be a biomarker for CDK4/6i response in ER$^+$ breast cancer.

LOSS OF FAT1 DRIVES RESISTANCE TO CDK4/6 INHIBITORS IN BREAST CANCER

CDK4/6 inhibitors (CDK4/6i) are part of the standard-of-care treatment for patients with estrogen receptor–positive (ER$^+$)/*HER2*$^-$ breast cancer. Recently, potential mechanisms of resistance to CDK4/6 inhibitors have been identified in both patient samples and preclinical models, including RB loss and *CDK6* amplification. To identify drivers of resistance to CDK4/6i, Li, Razavi, Li, and colleagues performed a genomic analysis of 348 post-CDK4/6i treated ER$^+$ breast tumors. Patients harboring *FAT1* loss-of-function mutations exhibited significantly decreased progression-free survival (PFS) compared with patients with missense *FAT1* mutations or wild-type *FAT1*, and a similar PFS as patients with deleterious *RB1* mutations. *FAT1*-deleted ER$^+$, CDK4/6i-sensitive breast cancer cell lines exhibited the same level of proliferation as the parental cell lines and, unlike the parental cell lines, did not exhibit any decrease in proliferation after treatment with a CDK4/6i. Phosphorylation of the CDK4/6 substrate RB was partially decreased in *FAT1*-deleted cells, and the IC_{50}s of CDK4/6is were significantly increased in *FAT1*-deleted cells compared to parental cells. Further, CDK6 levels were increased in *FAT1*-deleted cells and ER$^+$ tumors compared with wild-type *FAT1* parental cells and ER$^+$ tumors, respectively, and CDK6 levels were lower than CDK4 levels in parental cells and wild-type *FAT1* ER$^+$ tumors. Knockdown of *CDK6* in *FAT1*-deleted cells restored CDK4/6i sensitivity whereas overexpression of CDK6 led to resistance. The Hippo pathway, which has previously been shown to be a target of FAT1, was found to be suppressed in *FAT1*-deleted cells; moreover, *FAT1*-deleted cells exhibited increases in the binding of YAP/TAZ to TEAD sites in the *CDK6* promoter and the nuclear localization of YAP. Similarly, loss of *NF2*, a known regulator of Hippo signaling, resulted in increased CDK6 levels and CDK4/6i resistance in ER$^+$ breast cancer cells. These results identify *FAT1* loss–mediated CDK6 upregulation as a mechanism of CDK4/6i resistance and elucidate the role of Hippo signaling in ER$^+$ breast cancer. ■

Li Z, Razavi P, Li Q, Toy W, Liu B, Ping C, et al. Loss of the FAT1 tumor suppressor promotes resistance to CDK4/6 inhibitors via the Hippo pathway. Cancer Cell 2018;34:893–905.

AACR American Association for Cancer Research

CANCER DISCOVERY

Transcription Factor Motif Density Can Confer Transcriptional Addiction

Cancer Discov 2019;9:161. Published OnlineFirst December 14, 2018.