生命科学セミナー

Targeting transcriptional vulnerability by linked dependency in acute myeloid leukemia

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Cancer cells are addicted to their specific transcriptional programs for survival. A lineage-specific transcription factor MEF2C is aberrantly expressed in the MLL-rearranged subtype of acute myeloid leukemia (AML) and functions as a cooperating oncogene in this disease. Owing to the challenge of developing direct-acting small-molecule inhibitors of transcription factors, a therapeutic strategy for targeting MEF2C in leukemia has yet to be identified. We previously described domain-focused CRISPR screening, which is a genetic approach that nominates individual protein domains as cancer cell dependencies. In this study, we applied this method to kinase domains in search of therapeutically relevant dependencies in AML, and identified an essential requirement for LKB1 and its Salt-Inducible Kinase effectors to maintain the growth of AML lines that express MEF2C at high levels. Genetic and epigenomic analyses have revealed the mechanisms underlying these dependencies. Further, on-target chemical inhibition of SIK activity led to block of MEF2C function and significant delay in disease progression. This study highlights how an oncogenic transcription factor can be disabled by targeting of upstream kinases.

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