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HAEMATOLOGICAL CANCERS

Promising epigenetic targets in leukaemia identified

> "...inhibiting acetyl lysine binding by ENL might provide a therapeutic opportunity in leukaemia"

Epigenetic alterations are one of the hallmarks of cancer; the chromatin machinery is often exploited by cancer cells to change gene-expression patterns in order to alter the cellular phenotype. Histone modifications can be decoded by protein 'readers' that help orchestrate these cellular changes. Although potential targets have been identified, chromatin-regulating therapies for leukaemia are limited. In acute leukaemias, chromosomal rearrangements can lead to fusion of the mixed lineage leukaemia (MLL) protein with ENL or AF9, both of which have a conserved YEATS domain that can bind to acetylated lysines in histones. Two studies published in *Nature* reveal that ENL is a histone reader that promotes oncogenic transcription and, as a consequence, has potential as a target for epigenetic therapy.

Scott Armstrong, a corresponding author of one of the studies, elaborates: "we determined if ENL or AF9 might play an important role in leukaemia and, if so, whether this role is a result of binding acetylated histones". In terms of previous knowledge, although the YEATS domain was known to bind acetylated histones, "it was not known whether this domain had a role in cancer and, if so, which of the proteins associated with this domain are critical to its function," explains Armstrong. The researchers showed that ENL, but not AF9, was required for maintenance of acute myeloid leukaemia. CRISPR–Cas9-mediated depletion of ENL led to anti-leukaemic effects *in vitro* and *in vivo*. Biochemical and crystal structure analyses of the protein complexes showed that ENL binds to acetylated histone H3, and is localized to the promoter regions of actively transcribed genes involved in leukaemia development. Disruption of the interactions between the YEATS domain and acetylated histones, via structure-based mutagenesis, reduced RNA polymerase II binding to ENL-target genes, suppressing oncogenic activity *in vitro*. Crucially, prevention of ENL functionality sensitized leukaemic cells to bromodomain and extra-terminal (BET) inhibitors.

Armstrong remarks on the key findings: "We found that ENL is required for the maintenance of gene expression and cell proliferation associated with leukaemia, and that ENL maintains gene expression via binding to acetyl lysines. This function allows RNA polymerase II to gain access to and thereby alter the function of a subset of genes critical for leukaemia proliferation."

"Our study suggests that inhibiting acetyl lysine binding by ENL might provide a therapeutic opportunity in leukaemia. The structural work we describe sets the stage for the development of new small-molecule inhibitors. In addition, this work points to an important role for ENL and associated proteins in the control of RNA polymerase II function."

In another study, James Bradner and co-authors confirmed these findings. The researchers used CRISPR–Cas9 to perform a genomic loss-of-function screen in a leukaemic cell line, and showed that ENL was pathogenic *in vitro* and in a mouse leukaemic model. To understand the role of ENL in leukaemia pathogenesis, a chemical genetic strategy was used to achieve targeted protein degradation. Disrupting the interactions between the YEATS domain and acetylated histones via structure-based mutagenesis reduced RNA polymerase II recruitment to ENL target genes. Chromatin immunoprecipitation and next-generation DNA sequencing showed how much ENL was bound to DNA, and that an intact YEATS chromatin-reader domain was necessary to promote ENL-dependent leukaemic growth.

Collectively, these results indicate that ENL is a histone acetylation reader that regulates acute leukaemogenesis. Furthermore, displacement of ENL from chromatin might be a promising therapeutic strategy, either alone, or in combination with BET inhibitors. Finally, the mechanistic rationale for disrupting the YEATS domain paves the way for the development of new therapies for this dismal disease.

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ORIGINAL ARTICLES Wan, L. *et al.* ENL links histone acetylation to oncogenic gene expression in acute myeloid leukaemia. *Nature* http://dx.doi.org/10.1038/nature21687 (2017) | Erb, M. A. *et al.* Transcription control by the ENL YEATS domain in acute leukemia. *Nature* http://dx.doi.org/10.1038/nature21688 (2017)