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EPIGENETICS

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The presence of mixed lineage leukaemia (MLL) fusion proteins, generated from chromosomal translocations of *MLL1*, is a characteristic of acute leukaemias that confer poor prognosis. These chimaeric MLL proteins are transcriptional regulators that change the epigenetic landscape of the leukaemic cell to maintain the oncogenic state. Two papers have now independently identified ENL (also known as MLLT1) as being functionally important for the growth and maintenance of acute leukaemias.

Using CRISPR–Cas9-mediated gene editing in combination with competitive cell proliferation assays, both Wan, Wen, Li *et al.* and Erb *et al.* found that targeting the *ENL* gene could inhibit the outgrowth of a panel of acute leukaemia cell lines. ENL is a component of the super elongation complex (SEC) required to release paused RNA polymerase II (Pol II) for induction of rapid gene transcription, and has been previously reported to interact directly with the histone methyltransferase DOT1L. Interestingly, the requirement for ENL in acute leukaemia seems to be specific, as the depletion of the highly homologous AF9 was unable to suppress the growth of MLL-rearranged leukaemic cells. Confirming the *in vivo* relevance, both groups showed that in xenotransplantation mouse models of disseminated leukaemia, ENL loss in MV4;11 (MLL–AF4 rearranged acute myeloid leukaemia (AML)) or MOLM-13 cells (MLL–AF9 rearranged AML) slowed disease progression and was associated with prolonged survival.

Given that ENL is a transcriptional activator, both groups sought to identify the oncogenic gene expression programmes driven by ENL during acute leukaemia pathogenesis. Wan, Wen, Li *et al.* carried out RNA sequencing of MOLM-13 cells in which depletion of ENL could be induced, while Erb *et al.* used a novel chemical genetic strategy to promote pharmacological ENL degradation. Using these methods, the two groups converged on the observation that reducing ENL protein levels downregulated transcription of leukaemic drivers, such as MYC and leukaemic stem cell-associated genes, and upregulated myeloid differentiation markers.

Investigating further, they performed chromatin-immunoprecipitation and next-generation DNA sequencing (ChIP-seq) to show preferential enrichment of ENL at transcription start sites that correlated with an increased occupancy of Pol II at ENL target genes. Inactivation of ENL using either approach caused a loss of Pol II and cyclin-dependent kinase 9 (CDK9), the catalytic component of SEC, as well as decreased DOT1L-mediated histone methylation on ENL target genes. Therefore, ENL is required for the recruitment of Pol II transcriptional machinery to promote productive elongation.

ENL contains a YEATS (Yaf9, ENL, AF9, Taf14 and Sas5) domain, which has been shown to be a reader of lysine-acetylated histones in AF9. Histone peptide arrays validated the YEATS domain of ENL as being able to bind a subset of acetylated H3 histones including H3K27ac and H3K9ac. To test the hypothesis that the YEATS domain could be important in the chromatin localization of the Pol II transcriptional machinery, the two groups engineered mutations in ENL. Wan, Wen, Li *et al.* solved the co-crystal structure of the ENL YEATS domain bound to the H3K27ac peptide to inform the mutagenesis, while Erb *et al.* used the published structure of AF9. Both groups demonstrated that the acetyl-lysine binding-deficient ENL-Y78A mutant had reduced occupancy at ENL target genes, which correlated with decreased abundance of Pol II at these sites and an inability to rescue the changes in growth and differentiation associated with ENL loss.

> “the YEATS domain could be important in the chromatin localization of the Pol II transcriptional machinery”

The dependency of acute leukaemias on the reader function of the ENL YEATS domain prompted Wan, Wen, Li *et al.* to test the cooperation between ENL and bromodomain and extra-terminal domain-containing (BET) family members, where the bromodomain is an acetyl-lysine recognition motif, in sustaining oncogenic transcriptional pathways. Depletion of ENL was sufficient to increase the sensitivity of MLL-rearranged leukaemia cell lines to the BET bromodomain inhibitor JQ1. These data indicate that targeting the protein–protein interactions of ENL and other epigenetic readers through chromatin-competitive antagonists could have success as an anti-leukaemic therapy.

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ORIGINAL ARTICLES Erb, M. A. *et al.* Transcription control by the ENL YEATS domain in acute leukaemia. *Nature* **543**, 270–274 (2017) | Wan, L. *et al.* ENL links histone acetylation to oncogenic gene expression in acute myeloid leukaemia. *Nature* **543**, 265–269 (2017)