

UBE2E3 sustains PRC1.1 function and leukemic stemness in acute myeloid leukemia

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Abstract

Non-canonical Polycomb repressive complex 1 (ncPRC1) sustains leukemic stem cells and disease propagation in acute myeloid leukemia (AML), yet how its activity is preserved remains poorly understood. UBE2E3 is an E2 ubiquitin-conjugating enzyme and AML dependency of undefined function. Using proximity-dependent biotinylation and mass spectrometry, we identified UBE2E3 as a proximal interactor of multiple ncPRC1 components, including the PRC1.1 proteins BCOR, KDM2B and PCGF1, the PRC1.6 proteins MGA, L3MBTL2 and PCGF6, and the shared core proteins RING1A/B. Transcriptomic profiling after UBE2E3 depletion in AML recapitulated gene signatures of BCOR loss and revealed widespread deregulation of PRC1.1 target genes. Mechanistically, UBE2E3 depletion reduced BCOR and RING1B protein abundance while KDM2B, PCGF1 and PCGF6 were preserved. Re-expression of wild-type, but not catalytically dead, UBE2E3 restored RING1B abundance and normalized representative PRC1 target genes, demonstrating a requirement for E2 activity. Functionally, UBE2E3 depletion impaired AML cell proliferation, reduced clonogenic growth, induced differentiation-associated transcriptional programs and markedly diminished leukemic engraftment in xenograft models. These findings identify UBE2E3 as a previously unrecognized regulator of ncPRC1 function in AML. By maintaining the BCOR-RING1B axis of PRC1.1, UBE2E3 preserves leukemic stemness, clonogenicity and leukemia-initiating activity, linking ubiquitin signaling to Polycomb-dependent transcriptional control.

Introduction

Acute myeloid leukemia (AML) is a clonal myeloid malignancy in which uncontrolled proliferation, blocked differentiation and accumulation of immature progenitors drive disease. Despite decades of refinement of intensive chemotherapy and allogeneic stem-cell transplantation, relapse remains frequent and overall survival poor, and new molecular dependencies that sustain leukemic cell fitness are needed¹⁻³.

The ubiquitin proteasome system is a central regulator of protein homeostasis and signaling, controlling diverse cellular processes including cell cycle progression, DNA damage responses, transcriptional regulation, and chromatin dynamics⁴. Dysregulation of ubiquitin-dependent pathways is increasingly recognized as a driver of hematologic malignancies, however, mechanistic studies have largely focused on E3 ubiquitin ligases and deubiquitinases, whereas the contribution of E2 ubiquitin-conjugating enzymes remains comparatively understudied⁵⁻⁷. Emerging evidence suggests that E2 enzymes are not merely intermediates in ubiquitin transfer but can actively shape signaling outputs, cellular identity, and stem-cell fate decisions^{5,8,9}. Nevertheless, the role of most E2 enzymes in AML remains largely unknown.

UBE2E3 (ubiquitin-conjugating enzyme E2E3) is a class III E2 enzyme distinguished by an N-terminal extension that regulates its intracellular localization and substrate interactions. UBE2E3 has been implicated in cell-cycle progression, DNA damage responses, and ubiquitin-dependent regulation of

transcription factors, yet its biological function has been studied almost exclusively outside the hematopoietic system^{10–13}.

Here, we discovered that UBE2E3 is a regulator of non-canonical Polycomb formation. Using proximity proteomics, transcriptomic profiling, and functional genetic approaches, we demonstrate that UBE2E3 maintains the BCOR-RING1B axis of PRC1.1, thereby sustaining leukemic stemness, leukemia-initiating activity, and AML fitness.

Methods

A condensed summary follows; full procedures, antibodies, primer/shRNA sequences, plasmid construction, BioID and proteomics, RNA-seq, GSEA, in vivo assays and statistical methods are provided in **Supplemental Experimental Procedures**.

Cell lines and shRNA knockdown

OCI-AML2, NB4 and K562 cells were maintained in RPMI/10% FBS; HEK293T and Flp-In T-REx 293 in DMEM/10% FBS. TEX cells were maintained in IMDM/20% FBS with SCF (20 ng/mL) and IL-3 (2 ng/mL), and 8227 cells and primary AML cells in X-VIVO-10 with 20% BIT supplemented with Flt3-L, IL-6, SCF, TPO, IL-3 and G-CSF. Four independent shRNAs targeting human UBE2E3 (#5, #10, #11 and #21) were validated and used for knockdown (Fig. 5A); of these, the 5'-UTR-directed hairpin (sh UBE2E3 #21), which spares the UTR-less rescue transgenes, were used for the knockdown rescue experiments. Non-targeting hairpins served as controls. All constructs were delivered by lentiviral transduction (pLKO.1-puro; psPAX2/pCMV-VSV-G packaging) and selected with puromycin (1 µg/mL). Knockdown was confirmed by RT-qPCR and immunoblot

Proliferation, clonogenicity and knockdown-rescue

Proliferation was measured by trypan-blue exclusion (TC20, Bio-Rad); clonogenicity by methylcellulose colony formation over 10–14 days. For knockdown-rescue, cells were sequentially transduced with pLenti-FLAG-UBE2E3-WT, pLenti-FLAG-UBE2E3-C145S or empty vector, then with sh UBE2E3 #21 (5'-UTR-directed), which spares the transgene.

8227 cells and primary AML mononuclear cells transduced ex vivo with shUBE2E3 #21 or non-targeting control were transplanted into NOD/SCID-3/GM/SF (NS-GF; 8227) or NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (NSG; primary AML) mice; bone-marrow human engraftment was quantified by flow cytometry under approved institutional protocols.

Proteomics

The UBE2E3 proximity interactome was mapped by BioID in tetracycline-inducible Flp-In T-REx 293 cells expressing FLAG-BirA*-UBE2E3 versus FLAG-BirA*; biotinylated proteins were captured on streptavidin Sepharose and identified by LC-MS/MS as previously described, with high-confidence interactors filtered by SAINTexpress (BFDR ≤ 0.01)¹⁴. Prey-level output for all proteins detected in the BioID, including those below the significance threshold, is provided in Supplementary Table S3. Endogenous co-immunoprecipitation was performed in K562 cells.

Transcriptomics

Total RNA was extracted from OCI-AML2 cells 6 days post-transduction with sh UBE2E3 #21 or non-targeting control (n = 6 per arm); poly-A libraries were sequenced on Illumina, quantified against GENCODE Release 49 (GRCh38.p14) with Salmon, and differentially expressed genes called with DESeq2 (adjusted P < 0.05, with no fold-change threshold applied). Gene-set enrichment analysis (clusterProfiler, ranked by the DESeq2 stat) was performed against PRC1.1 target sets AML specific and overlapping (van den Boom *et al.*¹⁵), BCOR-KD in ESC (GSE104690, Wang *et al.*¹⁶), MGA loss in MOLM13 cells (GSE253748, Thomas *et al.*¹⁷), the LSC17 signature (Ng *et al.*¹⁸), Zeng *et al.* single-cell AML state signatures¹⁹, and the van Galen single-cell AML reference (GSE116256)²⁰.

Statistics and data availability

Data are mean $\pm$ SD of ≥ 3 biological replicates. Two-group comparisons used a two-tailed Student t-test, Mann-Whitney U test or Fisher's exact test; multi-group comparisons used ANOVA with appropriate post-hoc test. P < 0.05 was considered significant; where multiple categories were compared, P values were adjusted using the Benjamini-Hochberg method. RNA-seq data has been deposited at GEO (GSE343834). The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE²¹ partner repository with the dataset identifier PXD082589. BioID interactome is provided in **Supplementary Table S3** and the expression-proteomics protein report in **Supplementary Table S4**. Full reagent catalog numbers, primer/shRNA sequences and software versions are listed in Supplemental Experimental Procedures.

Results

UBE2E3 is elevated in poor-risk AML

UBE2E3 is a class III E2 enzyme whose functional importance in AML is unknown. To assess the relevance of UBE2E3 in AML, we examined its expression in primary patient samples and normal hematopoietic cells. UBE2E3 mRNA was higher in AML blasts than in normal bone-marrow mononuclear cells in both de novo (P = 8.6×10^{-5}) and relapsed (P = 0.0016) disease, and higher than in normal CD34 + progenitors in de novo AML (P = 0.0098, Fig. 1A). No significant differences in UBE2E3 expression were observed across morphologic subgroups of AML.

Among AML samples with increased UBE2E3, the favorable-risk fusion CBFB::MYH11 was significantly under-represented (adjusted $P = 0.038$), whereas GATA2::MECOM (adjusted $P = 0.157$) and ELN2017 adverse risk (as annotated in BeatAML 2.0, adjusted $P = 0.455$) showed enrichment that did not reach significance after correction for multiple testing (Fig. 1B). Together, these data indicate that high UBE2E3 expression is significantly under-represented among favorable-risk CBFB::MYH11 AML, with non-significant trends towards enrichment in higher-risk categories.

UBE2E3 physically associates with the identity subunits of both PRC1.1 and PRC1.6

To better understand the function of UBE2E3, we assessed UBE2E3's protein interactors using BioID coupled to mass spectrometry. Flag-BirA*-UBE2E3 was expressed in Flp-In T-REx 293 cells, and biotinylated proximal proteins were captured and identified by LC-MS/MS with statistical confidence assigned by SAINT (BFDR ≤ 0.01). Interestingly, the UBE2E3 interactome was enriched with chromatin-associated factors. Among these, two non-canonical PRC1 sub-complexes emerged as the top interactors (Fig. 2A).

Specifically, our BioID assay identified that UBE2E3 interacted with 5 of 10 known PRC1.1 subunits and 6 of 15 known PRC1.6 subunits, whereas interaction with PRC2 was minimally represented (Fig. 2B). Seven of 15 canonical PRC1 subunits were also identified as high-confidence interactors, consistent with the fact that canonical and non-canonical PRC1 share the RING1A/B catalytic core and several structural components. Thus, based on our BioID data we speculate that UBE2E3 engages the PRC1 family through this shared RING1A/B core, with the most complete coverage of the non-canonical PRC1.1 and PRC1.6 identity modules rather than of PRC2. Consistent with these findings, UBE2E3 localized to the nucleus in an IPO11-dependent manner (Fig. 2C), in keeping with its association with chromatin-associated ncPRC1 complexes.

To determine whether UBE2E3 marks a specific chromatin-regulatory state in AML, we analyzed its co-expression across an AML single-cell reference comprising 1,000 metacells, in which UBE2E3 was detected in 986 metacells. Across the full model, UBE2E3 expression correlated with a Trithorax/COMPASS transcriptional program, which promotes gene activation through H3K4 methylation. Specifically, UBE2E3 expression correlated with *KMT2C/MLL3* ($r = 0.54$), *KDM4C/JMJD2C* ($r = 0.49$), and a 22-gene Trithorax signature ($r = 0.61$; all P values below the limit of numerical precision; Pearson correlation across 1,000 metacells). Consistently, metacells in the top quartile of UBE2E3 expression showed marked enrichment of this program relative to the bottom quartile (Δ median + 0.95, + 1.77 and + 1.52 $\log_2$ units for the Trithorax signature, *KMT2C* and *KDM4C*, respectively; two-sided Mann-Whitney $P = 3.0 \times 10^{-58}$, 1.2×10^{-42} and 1.2×10^{-39} ; $n = 250$ metacells per group) (**Supplementary Figure S1**). In contrast, interrogation of the UBE2E3 proximity interactome identified no high-confidence interactions with COMPASS/Trithorax components, indicating that its association with the Trithorax program is transcriptional rather than physical.

We next sought to validate selected BioID interactions in leukemia cells using reciprocal co-immunoprecipitation. In K562 cells stably expressing HA-UBE2E3, anti-HA pull-downs recovered RING1A, while reciprocal immunoprecipitation of endogenous UBE2E3 confirmed its association with RING1B (Fig. 2D), supporting a physical association between UBE2E3 and the shared catalytic core of PRC1 complexes. Together, these findings support a model in which UBE2E3 associates with the RING1A/B catalytic core (Fig. 2E).

UBE2E3 depletion preferentially perturbs PRC1.1 regulated transcriptional programs

To determine whether the physical association of UBE2E3 with non-canonical PRC1 complexes translated into functional effects on gene regulation, we performed RNA-seq following UBE2E3 knockdown (KD) in OCI-AML2 cells and analyzed differential expression by GSEA (clusterProfiler; genes ranked by the DESeq2 Wald statistic; 17,090 detected genes). We interrogated three complementary reference categories: (i) the functional signature of BCOR loss (PRC1.1); (ii) ChIP-defined PRC1.1 target genes from primary AML; and (iii) functional signatures of MGA loss (PRC1.6).

Because BCOR is the defining regulatory component of PRC1.1, we first compared the UBE2E3-KD transcriptome with a published signature of BCOR loss derived from Wang et al. (2018, Cell Stem Cell; GEO: GSE104690). UBE2E3 knockdown produced a gene expression signature similar to that induced by BCOR loss. Specifically, genes that increased upon BCOR loss ($n = 1,088$) were also increased after UBE2E3 knockdown ($NES = +1.85$, $FDR = 2.04 \times 10^{-7}$; Fig. 3A), thus highlighting a close transcriptional relationship between UBE2E3 loss and disruption of PRC1.1 function.

To determine whether this relationship extended beyond a single dataset, we also examined a complementary and independent measure of PRC1.1 activity: genes directly occupied by PRC1.1 in primary AML. We analyzed the ChIP-seq-defined PRC1.1 target gene set reported by van den Boom et al. (2016), comprising 1,373 genes detectable in our dataset that are occupied by PRC1.1 in primary AML specimens and/or CD34⁺ progenitors. Within this set, 334 genes were significantly upregulated and 269 were downregulated following UBE2E3 depletion ($padj < 0.05$; Fig. 3B), indicating broad perturbation of PRC1.1-regulated transcriptional programs. Importantly, the substantial representation of bona fide PRC1.1 target genes among differentially expressed transcripts provides additional evidence linking UBE2E3 to the PRC1.1 regulatory network.

We next asked which biological programs were affected by UBE2E3 depletion. Hallmark pathway over-representation analysis was therefore performed separately on PRC1.1 target genes that were increased or decreased after UBE2E3 knockdown in AML cells (Fig. 3B, **bar plot**). PRC1.1 pathways increased after UBE2E3 knockdown included TGF- β signaling, reactive oxygen species, heme metabolism and the p53 pathway (all $FDR < 0.1$). In addition, pathways decreased after UBE2E3 knockdown included MYC targets V1, MYC targets V2, G2M checkpoint and E2F targets, indicating suppression of proliferative transcriptional programs.

Given the enrichment of PRC1.6 components in the BioID dataset, we next examined whether UBE2E3 depletion also recapitulated transcriptional consequences of PRC1.6 disruption. Genes increased following MGA knockout in MOLM-13 cells (Thomas et al., 2024; GSE253748; $n = 1,187$) were also increased after UBE2E3 depletion (NES = + 1.54, FDR = 4.24×10^{-5} ; Fig. 3C), although less strongly than the BCOR/PRC1.1 signature.

To determine whether transcriptional changes seen after UBE2E3 depletion were also reflected at the protein level, we performed quantitative proteomic profiling following UBE2E3 depletion in OCI-AML2 cells (8,655 proteins quantified; **Supplementary Table S4**). Proteomic analysis mirrored the transcriptomic findings, with stronger enrichment of the BCOR-loss signature (NES = + 1.87, FDR = 1.06×10^{-4}) and weaker enrichment of the MGA-loss signature (NES = + 1.67, FDR = 2.4×10^{-3}), while E2F and G2M checkpoint Hallmark programs were significantly depleted (Fig. 3D; **Supplementary Figure S2**). Together, these findings support a functional link between UBE2E3 and ncPRC1 complexes, with the BCOR/PRC1.1 signature more strongly enriched than the MGA/PRC1.6 signature in both the transcriptomic and proteomic datasets.

UBE2E3 maintains the abundance of PRC1.1 accessory subunits post-transcriptionally

The striking overlap between the UBE2E3-depletion and BCOR-loss signatures raised the possibility that UBE2E3 regulates the integrity of ncPRC1 complexes and the abundance of their subunits. Knockdown of UBE2E3 in OCI-AML2 cells led to a marked reduction in BCOR protein, together with reduced RING1B and, to a lesser extent, RING1A signal by immunoblot (Fig. 4A). In contrast, KDM2B was largely preserved, and the PRC1.1 subunit PCGF1 and the PRC1.6 subunit PCGF6 were unchanged (Fig. 4A), indicating that UBE2E3 loss does not deplete ncPRC1 subunits globally. MGA could not be detected reliably by immunoblot, but was not significantly reduced in the untargeted global proteome (log2 fold-change - 0.12; adjusted P = 0.51, quantified from 66 unique peptides; **Supplementary Table S4**).

To determine whether the observed protein changes reflected altered transcription, we examined subunit transcript levels in the UBE2E3-knockdown RNA-seq. None of BCOR, KDM2B, PCGF1, RING1A, RING1B, MGA or PCGF6 was differentially expressed (all adjusted P > 0.05; Fig. 4B), and RT-qPCR showed that BCOR and RING1B transcripts were unchanged or modestly increased despite reduced protein, whereas KDM2B transcript was reduced with sh UBE2E3 #10 but not #21 (Fig. 4C). KDM2B protein was preserved with both hairpins (Fig. 4A), arguing against a transcriptional mechanism. Together these data indicate that UBE2E3 maintains BCOR and RING1B protein levels post-transcriptionally. RING1A transcript showed a modest decrease that approached significance (log2 fold-change - 0.42; adjusted P = 0.055), so a partial transcriptional contribution to the reduction in RING1A protein cannot be excluded.

UBE2E3 regulates ncPRC1 function through its E2 catalytic activity

Because UBE2E3 functions as an E2 ubiquitin-conjugating enzyme, we next asked whether its role in the PRC1.1 pathway is dependent on its enzymatic activity. To address this question, we generated an enzymatically dead mutant (UBE2E3-C145S), in which the active-site cysteine was replaced by serine. OCI-AML2 cells were transduced with shRNA-resistant UBE2E3-WT or UBE2E3-C145S followed by depletion of endogenous UBE2E3.

Re-expression of UBE2E3-WT restored RING1B and RING1A protein signal (Fig. 4D) after UBE2E3 knockdown. Moreover, the wild type construct rescued expression of PRC1.1 and PRC1.6 regulated target genes (Fig. 4E). In contrast, the catalytic-dead UBE2E3-C145S mutant failed to rescue either RING1A or RING1B protein abundance (Fig. 4D) or PRC1.1 and PRC1.6 target gene expression (Fig. 4E). Thus, the enzymatic activity of UBE2E3 is required to support the function of the PRC1.1 and PRC1.6 complexes.

UBE2E3 is required for AML growth, clonogenicity and leukemia-initiating activity

Having established a role for UBE2E3 in maintaining ncPRC1 function, we next examined the consequences of UBE2E3 loss on AML cell fitness and leukemia stem cell properties. UBE2E3 knockdown reduced proliferation of AML cells (OCI-AML2, NB4) (Fig. 5A, B). Notably, the effects of UBE2E3 knockdown on AML proliferation were rescued with wild-type but not catalytic-dead UBE2E3 (C145S), thus demonstrating on-target specificity of the knockdown as well as the dependence on its enzymatic activity (**Supplementary Figure S3**). Furthermore, UBE2E3 knockdown reduced the clonogenic growth of AML cell lines (OCI-AML2 and NB4, Fig. 5C).

TEX cells have properties of AML stem cells, including hierarchical structure and the ability to engraft into mouse marrow. 8227 cells are a low passage primary AML culture model that are arranged in a hierarchy with the stem cells located in the CD34 + CD38⁻ fraction. Knockdown of UBE2E3 also reduced colony formation of both TEX and 8227 cells (Fig. 5D). In accord, UBE2E3KD also upregulated gene expression signatures associated with differentiation while depleting progenitor-associated signatures (Fig. 5E, **Supplementary Figure S4**).

Finally, we tested the effects of UBE2E3 depletion on AML engraftment into mouse marrow. In 8227 cells, UBE2E3 depletion reduced bone marrow engraftment (Fig. 5F). Primary AML cells were transduced ex vivo with shRNA targeting UBE2E3 or control sequences and transplanted into NSG mice. Knockdown of UBE2E3 profoundly reduced leukemic engraftment compared with control-transduced cells (Fig. 5G, **left**). The marked reduction in leukemic engraftment was maintained upon secondary transplantation (Fig. 5G, **right**), providing evidence that UBE2E3 is required for the maintenance of leukemia stem cell function.

Together, these data establish UBE2E3 as a critical regulator of AML fitness. Loss of UBE2E3 impairs proliferation, clonogenic growth, and leukemic engraftment while promoting transcriptional programs associated with differentiation and loss of stem cell identity (Fig. 5H).

Discussion

In this study, we identify UBE2E3 as a previously unrecognized regulator of non-canonical Polycomb function in AML. We demonstrate that UBE2E3 localizes to the nucleus in an IPO11-dependent manner and associates with both PRC1.1 and PRC1.6 through the shared RING1A/B catalytic core. However, the strongest mechanistic and functional evidence emerging from our work converged on the BCOR–RING1B axis of PRC1.1. Loss of UBE2E3 reduced the abundance of PRC1.1 accessory subunits, including BCOR and RING1B, disrupted PRC1.1-associated transcriptional programs, and promoted loss of leukemic stemness accompanied by impaired proliferation, clonogenic growth, and leukemic engraftment. Collectively, these findings position UBE2E3 as an upstream regulator of ncPRC1-dependent transcriptional networks that sustain AML cell identity and fitness.

Although dysregulation of the ubiquitin-proteasome system is a hallmark of hematologic malignancies, the contribution of E2 ubiquitin-conjugating enzymes to leukemia biology remains incompletely understood²². Most mechanistic and therapeutic efforts have focused on E3 ligases and deubiquitinases, whereas E2 enzymes have traditionally been viewed as passive intermediates in ubiquitin transfer. This view has evolved considerably over the last decade, with increasing evidence that E2 enzymes actively shape ubiquitin signaling, influence substrate specificity, and regulate cell fate decisions⁵. In leukemia, only a limited number of E2 enzymes have been functionally implicated. UBE2S has been linked to maintenance of stemness-associated programs and adverse disease biology across multiple malignancies⁸, while recent studies identified UBE2G1 as a regulator of hematopoietic stem-cell aging and myeloid-biased differentiation^{6,7}. Together, these studies suggest that E2 enzymes influence cellular identity and lineage specification beyond their canonical role in protein turnover. Our findings extend this concept by identifying a direct connection between an E2 enzyme and Polycomb-mediated regulation of leukemic cell state.

A central observation of our study is the convergence of independent proteomic, biochemical, transcriptomic, and functional datasets on non-canonical PRC1 biology. Polycomb complexes were originally viewed primarily as developmental repressors acting downstream of PRC2-mediated H3K27 methylation^{16,23,24}. However, this paradigm has shifted with the recognition that non-canonical PRC1 complexes regulate stem-cell identity and malignant self-renewal through mechanisms that are, at least in part, independent of classical PRC2-mediated repression. Among these complexes, PRC1.1 has emerged as a critical regulator of AML biology. The seminal work of van den Boom and colleagues demonstrated that PRC1.1 is essential for leukemic stem-cell maintenance and AML propagation and occupies a distinct set of actively transcribed loci involved in metabolism, biosynthetic fitness, and leukemia maintenance¹⁵. Subsequent studies established that disruption of KDM2B-dependent PRC1.1 function compromises leukemic self-renewal and leukemia maintenance *in vivo*²⁵. Together, these findings position PRC1.1 as a central regulator of leukemic cell identity rather than merely a developmental silencing complex. The biological consequences of UBE2E3 depletion closely mirror the emerging understanding of PRC1.1 function in AML. UBE2E3 depletion reduced BCOR and RING1B

protein abundance and was accompanied by enrichment of BCOR-loss signatures and widespread deregulation of genes previously shown to be occupied and regulated by PRC1.1 in AML. Moreover, loss of UBE2E3 impaired clonogenicity, markedly reduced leukemic engraftment, and induced a coordinated shift away from progenitor-like and leukemia stem-cell transcriptional programs toward monocyte-like associated states.

Our co-expression analysis further places UBE2E3 within an actively transcribed, MLL/HOXA-associated AML state enriched for a Trithorax/COMPASS transcriptional program^{26,27}. Interestingly, although UBE2E3 expression closely tracks with this transcriptional state, its physical interactions were restricted to PRC1.1 and PRC1.6 rather than COMPASS components. This selective association is consistent with the emerging role of non-canonical PRC1.1 at actively transcribed loci in AML and suggests that UBE2E3 supports Polycomb function within a transcriptionally permissive chromatin environment, thereby helping preserve leukemic stem-cell identity.

The clinical relevance of this pathway has become increasingly apparent with the development of therapies targeting transcriptional dependencies in AML. Recent studies indicate that PRC1.1 occupies chromatin regions intersecting with DOT1L- and menin-regulated transcriptional programs and may influence responses to these therapies^{28,29}. These observations place PRC1.1 at the center of the epigenetic circuitry that maintains HOXA/MEIS1-driven leukemia and suggest that modulation of PRC1.1 activity may influence therapeutic response. In this context, our identification of UBE2E3 as a regulator of the BCOR-RING1B axis raises the possibility that ubiquitin-dependent control of PRC1.1 abundance represents an additional layer governing epigenetic plasticity in AML. Whether UBE2E3 expression or activity influences sensitivity to menin- or DOT1L-directed therapies will be an important question for future studies.

In summary, we identify UBE2E3 as a previously unrecognized regulator of non-canonical PRC1 function in AML. Through maintenance of the BCOR-RING1B axis, UBE2E3 preserves leukemic stemness programs, clonogenic potential, and leukemia-initiating activity. These findings establish a mechanistic link between ubiquitin signaling and Polycomb-mediated transcriptional control and nominate UBE2E3 as a potential therapeutic vulnerability in AML.

Declarations

Author Contributions: V.G. designed and performed the majority of the experiments, analyzed and interpreted the data, prepared the figures, and contributed to manuscript writing. A.Hi. designed and performed experiments, analyzed data, and contributed to data interpretation. M.A., R.P., N.S., E.K., and A.Ha. performed selected experiments and contributed to data acquisition and analysis. N.G.E.Z., R.H., L.D., Y.Y., and M.G. conducted and analyzed in vivo studies. A.A. and M.A.P. provided primary AML patient samples, clinical annotation, and contributed to data interpretation. J.S.G. and B.R. designed and analyzed proteomic experiments. L.S. and G.F. contributed to experimental design, interpretation of results, and scientific discussion. R.W. provided expertise in ubiquitin biology and enzymology and

contributed to experimental design and data interpretation. V.V. and G.D.B. contributed to bioinformatic and transcriptomic data analysis and interpretation. A.D.S. and B.N. conceived and supervised the study, designed experiments, interpreted data, secured funding, and wrote the manuscript. All authors reviewed, edited, and approved the final manuscript.

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Competing Interests: B.N. has received honoraria from Medison, Bristol Myers Squibb (BMS), and Stemline Therapeutics. A.D.S has received research funding from Takeda Pharmaceuticals, BMS and Medivir AB, and consulting fees/honorarium from Takeda, Novartis, Jazz, and Otsuka Pharmaceuticals. ADS is named on a patent application for the use of DNT cells to treat AML. ADS is a member of the Medical and Scientific Advisory Board of the Leukemia and Lymphoma Society of Canada. The remaining authors declare no competing financial interests.

Ethics: The University Health Network institutional review boards approved the collection and use of human tissue for this study (Research Ethics Board protocol #13-7163). All human samples were collected with written informed consent in accordance with the Declaration of Helsinki. All animal studies were performed in accordance with University Health Network Animal Use Protocol 1251.

Data Availability Statement: RNA-sequencing data have been deposited in the Gene Expression Omnibus under accession GSE343834, and the quantitative (expression) mass-spectrometry proteomics data in ProteomeXchange/PRIDE under accession PXD082589. The processed UBE2E3 BioID proximity interactome (per-replicate spectral counts, SAINTexpress scores and BFDR values for all detected prey proteins, together with the unfiltered SAINTexpress output and the full spectral-count matrix) is provided in Supplementary Table S3, and the full quantitative (expression) proteomics protein report in Supplementary Table S4. Additional data are available from the corresponding author on reasonable request.

Use of AI-assisted technologies:

Artificial intelligence (AI)-assisted tools were used for limited purposes: Large language model-based tools were used to draft and refine the plotting code used to render Figures 2B, 3D and 4B from author-generated source data, and to edit the grammar and language of the manuscript text. No figure content, image or data were generated by AI, and the underlying source data for these panels are provided. AI tools were not used for study design, data generation, or data analysis and interpretation. All authors

reviewed and verified the resulting figures and text and take full responsibility for the integrity and accuracy of the work.

References

1. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H *et al.* Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022; 140: 1345–1377.
2. Nachmias B, Aumann S, Haran A, Schimmer AD. Venetoclax resistance in acute myeloid leukaemia- Clinical and biological insights. *Br J Haematol* 2024; 204: 1146–1158.
3. Thomas D, Majeti R. Biology and relevance of human acute myeloid leukemia stem cells. *Blood* 2017; 129: 1577–1585.
4. Damgaard RB. The ubiquitin system: from cell signalling to disease biology and new therapeutic opportunities. *Cell Death Differ* 2021; 28: 423–426.
5. Stewart MD, Ritterhoff T, Klevit RE, Brzovic PS. E2 enzymes: more than just middle men. *Cell Res* 2016; 26: 423–440.
6. Miller V, Nachmias B. Proteostasis meets signaling: UBE2G1 in hematopoietic stem cell aging. *Haematologica* 2026. doi:10.3324/haematol.2026.300724.
7. Niemann J, Schuster T, Sakk V, Soller K, Brown A, Wiese S *et al.* Elevated levels of Ube2g1 in hematopoietic stem cells lead to segmental aging of the hematopoietic system. *Haematologica* 2026. doi:10.3324/haematol.2025.288847.
8. Bao H, Luo Y, Ding G, Fu Z. A Pan-Cancer Analysis of UBE2S in Tumorigenesis, Prognosis, Pathway, Immune Infiltration and Evasion, and Therapy Response from an Immune-Oncology Perspective. *J Oncol* 2022; 2022: 1–35.
9. Luo H, Qin Y, Reu F, Ye S, Dai Y, Huang J *et al.* Microarray-based analysis and clinical validation identify ubiquitin-conjugating enzyme E2E1 (UBE2E1) as a prognostic factor in acute myeloid leukemia. *J Hematol Oncol* 2016; 9: 125.
10. Plafker KS, Farjo KM, Wiechmann AF, Plafker SM. The human ubiquitin conjugating enzyme, UBE2E3, is required for proliferation of retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 2008; 49: 5611–5618.
11. Plafker KS, Zyla K, Berry W, Plafker SM. Loss of the ubiquitin conjugating enzyme UBE2E3 induces cellular senescence. *Redox Biol* 2018; 17: 411–422.
12. Daou S, Barbour H, Ahmed O, Masclef L, Baril C, Sen Nkwe N *et al.* Monoubiquitination of ASXLs controls the deubiquitinase activity of the tumor suppressor BAP1. *Nat Commun* 2018; 9: 4385.
13. Plafker SM, Macara IG. Importin-11, a nuclear import receptor for the ubiquitin-conjugating enzyme, UbcM2. *EMBO J* 2000; 19: 5502–5513.
14. Nachmias B, Khan DH, Voisin V, Mer AS, Thomas GE, Segev N *et al.* IPO11 regulates the nuclear import of BZW1/2 and is necessary for AML cells and stem cells. *Leukemia* 2022; 36: 1283–1295.

15. van den Boom V, Maat H, Geugien M, Rodríguez López A, Sotoca AM, Jaques J et al. Non-canonical PRC1.1 Targets Active Genes Independent of H3K27me3 and Is Essential for Leukemogenesis. *Cell Rep* 2016; 14: 332–346.
16. Wang Z, Gearhart MD, Lee Y-W, Kumar I, Ramazanov B, Zhang Y et al. A Non-canonical BCOR-PRC1.1 Complex Represses Differentiation Programs in Human ESCs. *Cell Stem Cell* 2018; 22: 235–251.e9.
17. Thomas ME, Qi W, Walsh MP, Ma J, Westover T, Abdelhamed S et al. Functional characterization of cooperating MGA mutations in RUNX1::RUNX1T1 acute myeloid leukemia. *Leukemia* 2024; 38: 991–1002.
18. Ng SWK, Mitchell A, Kennedy JA, Chen WC, McLeod J, Ibrahimova N et al. A 17-gene stemness score for rapid determination of risk in acute leukaemia. *Nature* 2016; 540: 433–437.
19. Zeng AGX, Bansal S, Jin L, Mitchell A, Chen WC, Abbas HA et al. A cellular hierarchy framework for understanding heterogeneity and predicting drug response in acute myeloid leukemia. *Nat Med* 2022; 28: 1212–1223.
20. van Galen P, Hovestadt V, Wadsworth li MH, Hughes TK, Griffin GK, Battaglia S et al. Single-Cell RNA-Seq Reveals AML Hierarchies Relevant to Disease Progression and Immunity. *Cell* 2019; 176: 1265–1281.e24.
21. Perez-Riverol Y, Bandla C, Kundu DJ, Kamatchinathan S, Bai J, Hewapathirana S et al. The PRIDE database at 20 years: 2025 update. *Nucleic Acids Res* 2025; 53: D543–D553.
22. Di Costanzo A, Del Gaudio N, Conte L, Altucci L. The Ubiquitin Proteasome System in Hematological Malignancies: New Insight into Its Functional Role and Therapeutic Options. *Cancers* 2020; 12: 1898.
23. Geng Z, Gao Z. Mammalian PRC1 Complexes: Compositional Complexity and Diverse Molecular Mechanisms. *Int J Mol Sci* 2020; 21: 8594.
24. Wang W, Qin J-J, Voruganti S, Nag S, Zhou J, Zhang R. Polycomb Group (PcG) Proteins and Human Cancers: Multifaceted Functions and Therapeutic Implications. *Med Res Rev* 2015; 35: 1220–1267.
25. He J, Nguyen AT, Zhang Y. KDM2b/JHDM1b, an H3K36me2-specific demethylase, is required for initiation and maintenance of acute myeloid leukemia. *Blood* 2011; 117: 3869–3880.
26. Schuettengruber B, Bourbon H-M, Di Croce L, Cavalli G. Genome Regulation by Polycomb and Trithorax: 70 Years and Counting. *Cell* 2017; 171: 34–57.
27. Piunti A, Shilatifard A. Epigenetic balance of gene expression by Polycomb and COMPASS families. *Science* 2016; 352: aad9780.
28. Zhou X, Zhang L, Aryal S, Veasey V, Tajik A, Restelli C et al. Epigenetic regulation of noncanonical menin targets modulates menin inhibitor response in acute myeloid leukemia. *Blood* 2024; 144: 2018–2032.
29. Neville D, Ferguson DT, Heikamp EB, Lai Z, Magor GW, Lam C et al. DOT1L provides transcriptional memory through PRC1.1 antagonism. *Nat Cell Biol* 2026; 28: 307–322.

Figures

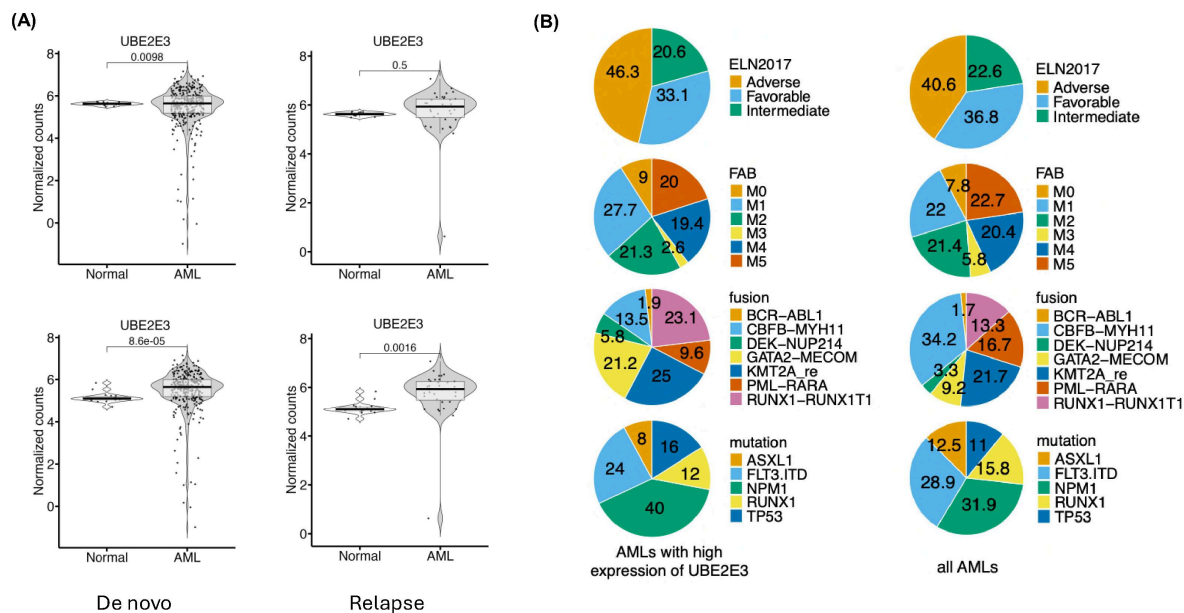


Figure 1

Figure 1

UBE2E3 is elevated in poor risk AML.

(A) UBE2E3 normalized expression in normal CD34⁺ cells (upper panel) and normal mononuclear samples (lower panel) versus AML blasts in the Beat AML dataset. Columns correspond to de novo and relapse AML subgroups. Box-and-violin plots; each dot represents one sample; P values by 2-tailed Student t test.

(B) Clinical and molecular composition of AML cases with high UBE2E3 expression (left; high UBE2E3) compared with the entire cohort (right; all AMLs) in the Beat AML dataset. Pie charts show the proportion of cases in each category and changes in proportions relative to all AMLs were tested using Fisher's exact test with Benjamini-Hochberg correction for multiple testing; Benjamini-Hochberg-adjusted P values are reported in the Results text.

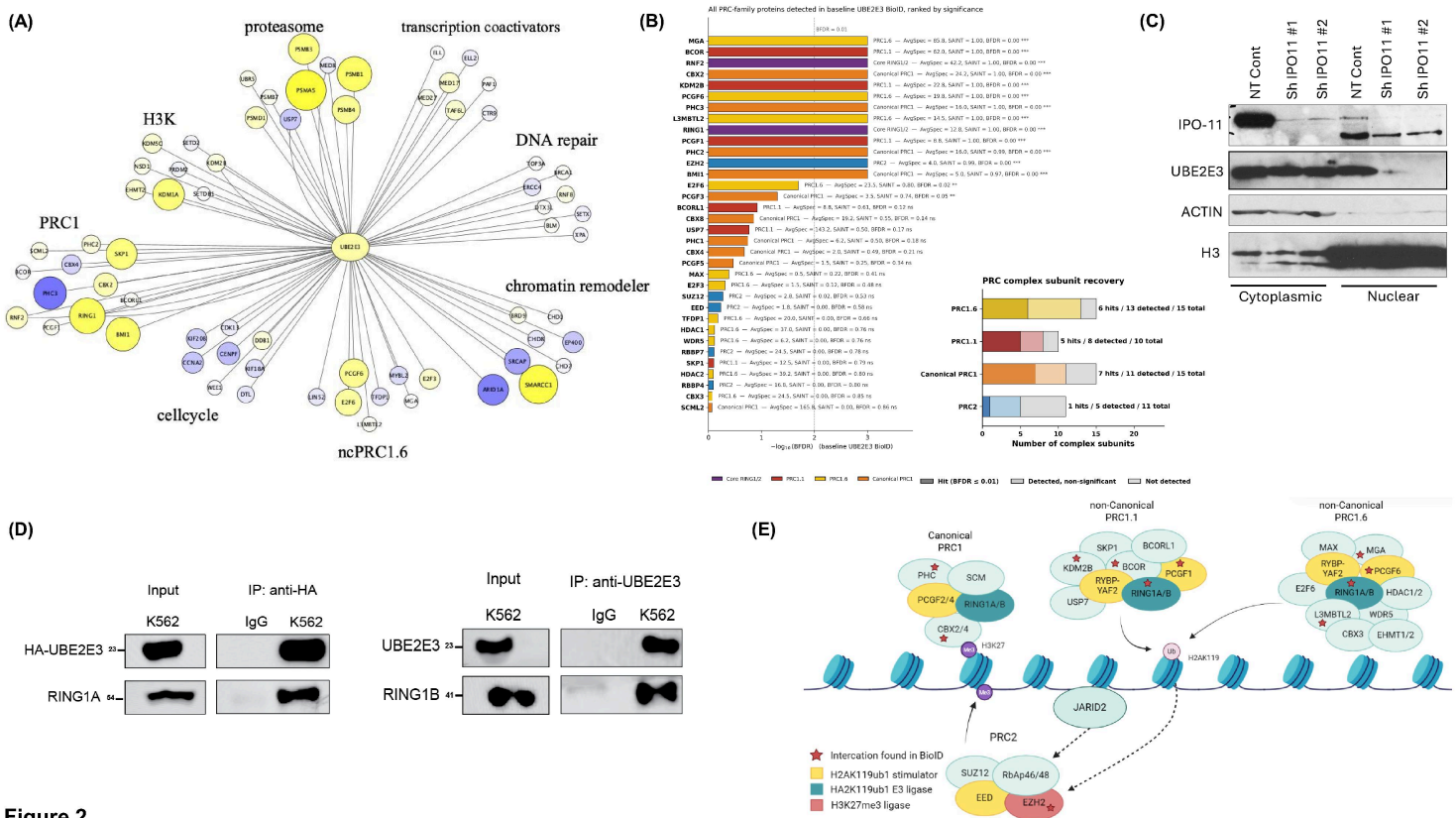


Figure 2

Figure 2

UBE2E3 associates with non-canonical PRC1 complexes through the shared RING1A/B catalytic core.

(A) Network representation of proteins identified by UBE2E3 BioID proximity proteomics, organized according to protein complex membership (BFDR ≤ 0.01). The yellow color versus blue represents a high expression of the interactor in BeatAML vs. bone marrow mononuclear cells.

(B) Left, forest plot showing enrichment of PRC-family proteins identified by BioID, ranked according to significance and annotated by complex membership. Right, summary of PRC complex components classified as significant interactors, detected but non-significant proteins, or not detected. BioID was performed in two independent biological pools per condition, each analyzed in two technical replicates; high-confidence interactors were defined by SAINTexpress BFDR ≤ 0.01 against the FLAG-BirA* control.

(C) Cytoplasmic and nuclear fractionation of OCI-AML2 cells demonstrating the subcellular localization of UBE2E3 following knockdown of IPO11 with two independent shRNAs. Actin is a cytoplasmic marker, H3 (histone 3) is a nuclear marker. Blots are representative of n = 2 independent experiments.

(D) Reciprocal co-immunoprecipitation in K562 cells. Left, anti-HA immunoprecipitation of HA-tagged UBE2E3 followed by immunoblotting for HA-UBE2E3 and RING1A. Right, immunoprecipitation of endogenous UBE2E3 followed by immunoblotting for UBE2E3 and RING1B. Input lanes are shown alongside each immunoprecipitation. IgG served as an isotype control. Blots are representative of n = 2 independent experiments.

(E) Schematic representation of canonical PRC1, non-canonical PRC1.1 and PRC1.6, and PRC2. Components identified as UBE2E3 BioID proximity interactors are marked with red stars.

Abbreviations: ACTIN, beta-actin; BCOR, BCL6 corepressor; BFDR, Bayesian false discovery rate; BioID, proximity-dependent biotinylation; HA, hemagglutinin; IPO11, importin-11; KDM2B, lysine demethylase 2B; ncPRC1, non-canonical Polycomb repressive complex 1; PRC, Polycomb repressive complex.

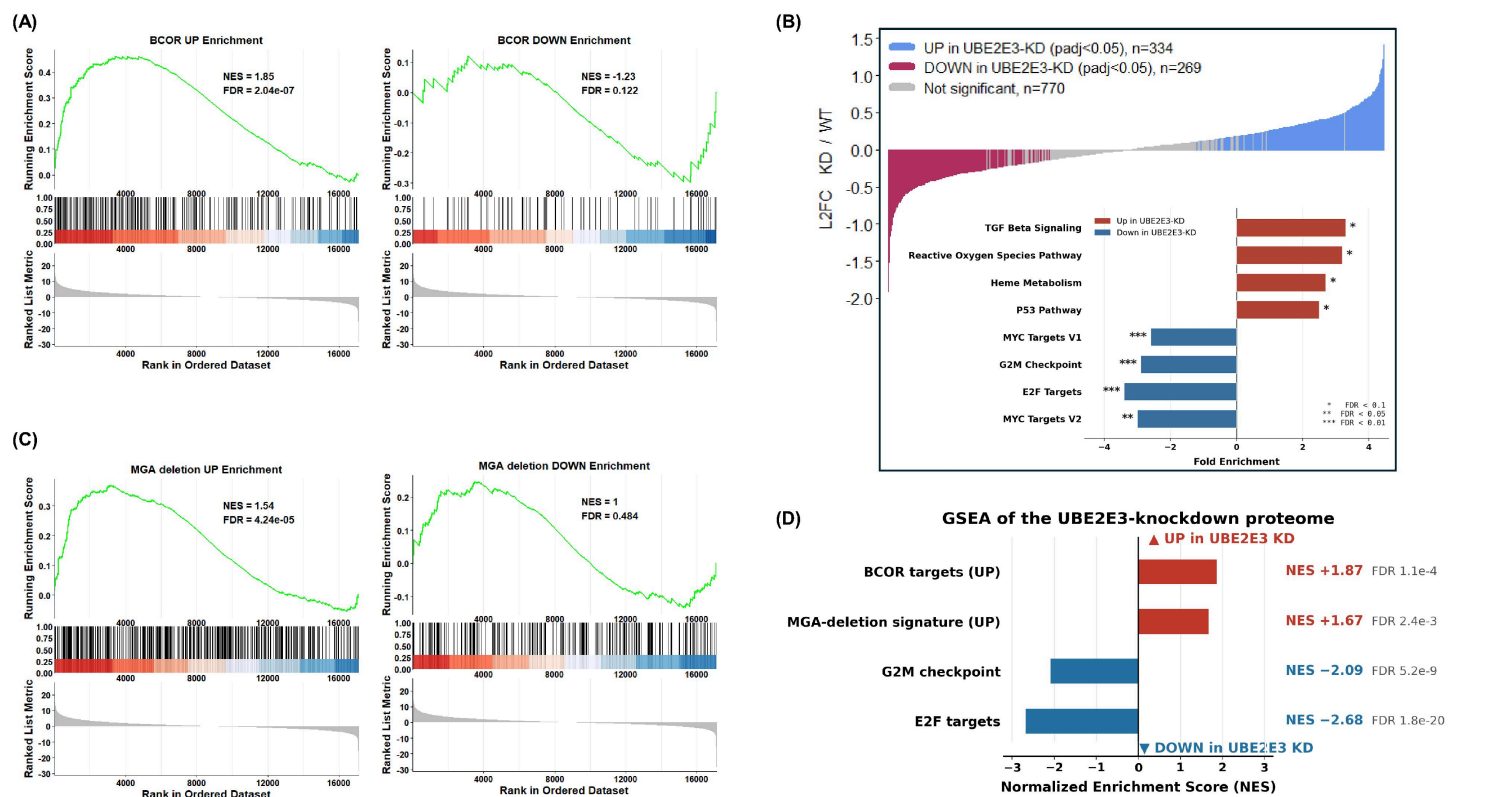


Figure 3

Figure 3

UBE2E3 depletion recapitulates transcriptional programs associated with PRC1.1 and PRC1.6 disruption.

(A) GSEA (clusterProfiler) of the ranked UBE2E3-knockdown OCI-AML2 transcriptome against the BCOR-loss signature (Wang et al., 2018; GSE104690). Left, genes de-repressed (up-regulated) upon BCOR knockdown, which are significantly enriched among UBE2E3-KD up-regulated genes; right, genes repressed (down-regulated) upon BCOR knockdown, shown for completeness and not statistically significant. Enrichment of the de-repressed set indicates loss of PRC1.1-mediated repression following UBE2E3 knockdown. RNA-seq comprised n = 6 biological replicates per arm; genes were ranked by the DESeq2 Wald statistic.

(B) Expression changes of PRC1.1 target genes defined by PRC1.1 ChIP-seq in primary AML and CD34+ hematopoietic progenitors (van den Boom et al., 2016). Bars represent log2 fold-change following UBE2E3 depletion. Blue, significantly upregulated; red, significantly downregulated; grey, not significant

(adjusted $P > 0.05$). Inset, MSigDB Hallmark (v2026.1) over-representation analysis (ORA) of van den Boom PRC1.1 AML target genes (AML-specific plus overlapping; 1,373 detected) that were significantly up- or down-regulated after UBE2E3 knockdown (DESeq2 adjusted $P < 0.05$). * FDR < 0.1; ** FDR < 0.05; *** FDR < 0.01.

(C) GSEA (clusterProfiler) against the MGA-loss signature (Thomas et al., 2024; GSE253748). Left, genes de-repressed (up-regulated) upon MGA knockout in MOLM-13 cells, which are enriched among UBE2E3-KD up-regulated genes; right, genes repressed (down-regulated) upon MGA knockout, shown for completeness and not statistically significant. The de-repressed enrichment is consistently weaker than for the BCOR/PRC1.1 signature.

(D) Summary of GSEA (clusterProfiler) on the UBE2E3-knockdown expression-proteomics data, with proteins ranked by log2 fold-change and tested against the BCOR-loss, MGA-loss signatures, E2F and G2/M signatures. Bars indicate normalized enrichment scores (NES); red, positive enrichment; blue, negative enrichment. Detailed enrichment plots are shown in Supplementary Figure S2. Expression proteomics comprised $n = 3$ biological replicates per arm. The underlying protein report is provided in Supplementary Table S4.

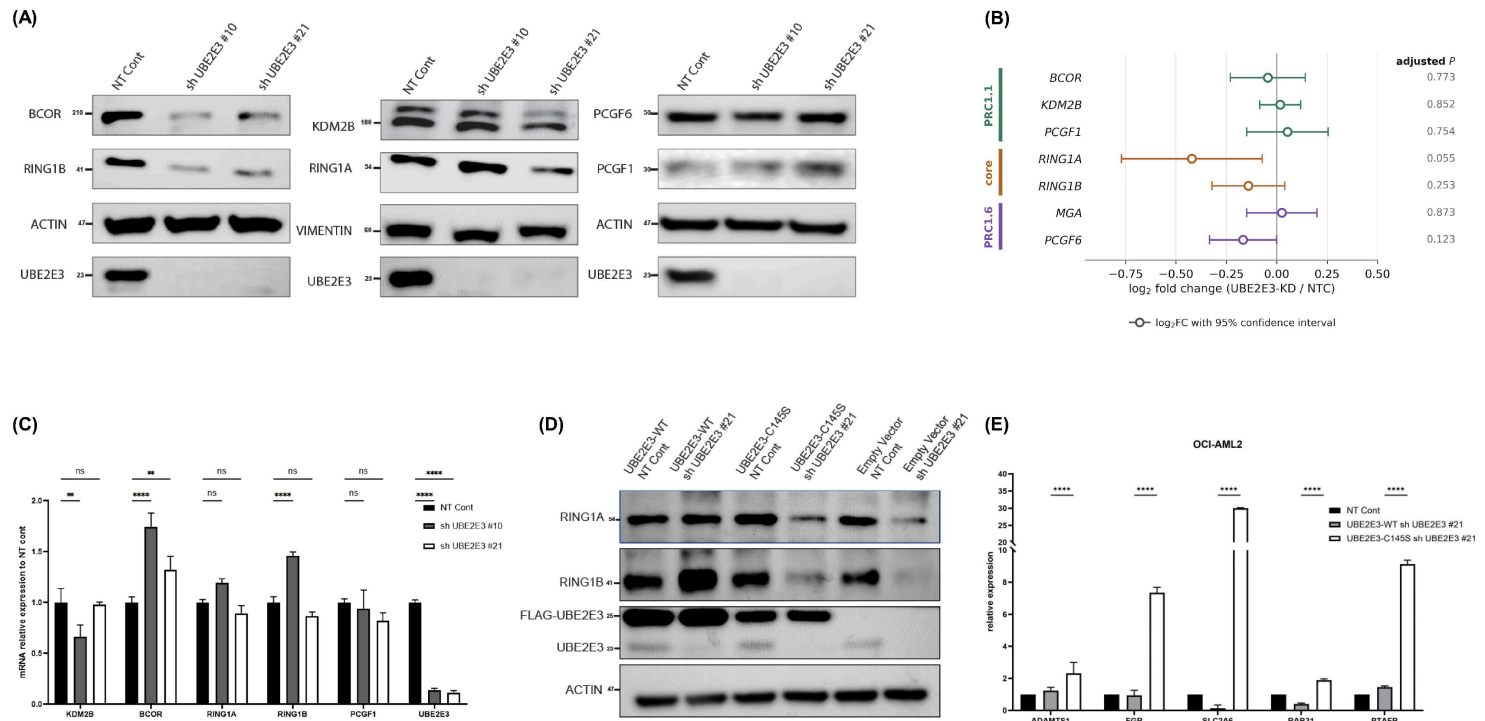


Figure 4

Figure 4

UBE2E3 catalytic activity is required for maintenance of the BCOR-RING1B axis of PRC1.1.

(A) Immunoblot analysis of ncPRC1 subunits in OCI-AML2 cells expressing non-targeting control (NT Cont) or two independent UBE2E3-targeting shRNAs (sh UBE2E3 #10 and #21). Membranes were probed for BCOR and RING1B (left), KDM2B and RING1A (centre), and PCGF6 and PCGF1 (right); ACTIN (left and right blots) and VIMENTIN (centre blot) served as loading controls, and UBE2E3 confirms knockdown in each experiment. Blots are representative of n = 3 independent experiments.

(B) Transcript-level changes for the subunits examined in (A), plus MGA, from RNA-seq of OCI-AML2 cells following UBE2E3 knockdown (n = 6 biological replicates per arm; DESeq2). Points show log2 fold change with 95% confidence intervals; Benjamini-Hochberg adjusted P values are shown at right. Subunits are grouped as PRC1.1, the shared RING1A/B catalytic core, and PRC1.6. No subunit was differentially expressed. UBE2E3 knockdown was confirmed in the same dataset (log2 fold-change -4.24; adjusted P = 1.0×10^{-175}).

(C) RT-qPCR analysis of ncPRC1 subunit transcripts (KDM2B, BCOR, RING1A, RING1B, PCGF1) and UBE2E3 in control and UBE2E3-depleted OCI-AML2 cells. Expression is normalized to control cells. Data are mean $\pm$ SD of three biological replicates, each assayed in technical triplicate; each shRNA was compared with the non-targeting control. ns, not significant; **P < 0.01; ****P < 0.0001.

(D) Rescue experiment in OCI-AML2 cells expressing UBE2E3 shRNA and reconstituted with shRNA-resistant wild-type UBE2E3 (WT), catalytic-dead UBE2E3-C145S, or empty vector. Immunoblot analysis of RING1A, RING1B, FLAG-tagged (transgene) and endogenous UBE2E3; ACTIN served as the loading control. Blots are representative of n = 3 independent experiments.

(E) RT-qPCR of representative PRC1 target genes after rescue with wild-type or catalytic-dead UBE2E3: *ADAMTS1* and *RAB31* (up-regulated in both BCOR-knockdown and MGA-knockout signatures) and *FGR*, *PTAFR* and *SLC2A6* (up-regulated in the MGA-knockout signature). Data are mean $\pm$ SD of three biological replicates.

Abbreviations: BCOR, BCL6 corepressor; C145S, catalytic-dead UBE2E3 (Cys145Ser); KD, knockdown; KDM2B, lysine demethylase 2B; MGA, MAX dimerization protein; ncPRC1, non-canonical Polycomb repressive complex 1; NT, non-targeting; PCGF1, Polycomb group ring finger 1; PCGF6, Polycomb group ring finger 6; PRC, Polycomb repressive complex; RING1A/B, E3 ubiquitin-protein ligases RING1 and RNF2; RT-qPCR, reverse-transcription quantitative PCR; WT, wild-type.

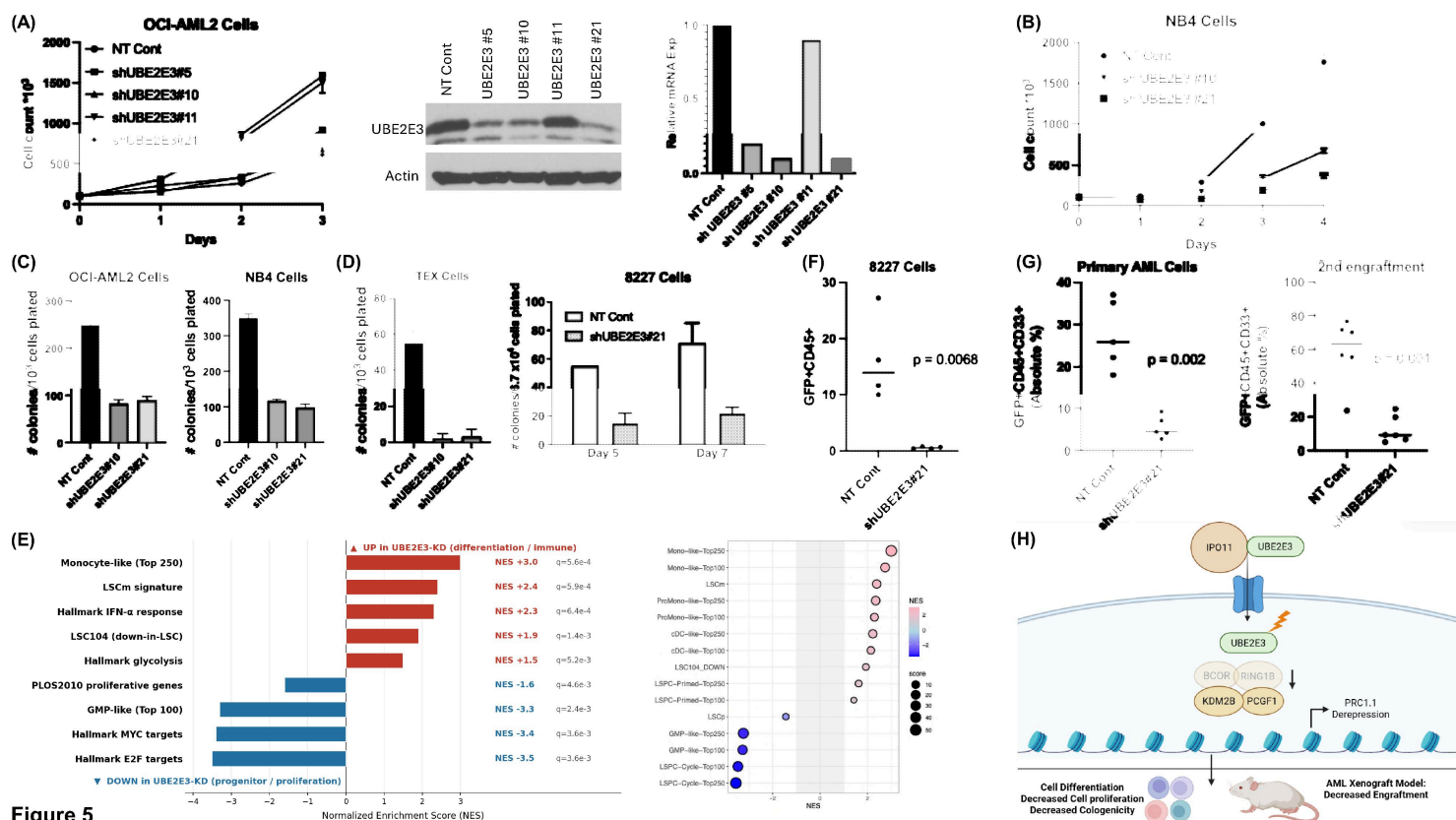


Figure 5

Figure 5

UBE2E3 is required for AML growth, leukemia-initiating activity, and maintenance of stemness-associated transcriptional programs.

(A) Cell growth and viability assay in OCI-AML2 cells transduced with non-targeting control (NTC) or four independent UBE2E3-targeting shRNAs. Cell growth was monitored over time. Immunoblot and RT-qPCR analysis confirming UBE2E3 depletion are shown on the right. Data are presented as mean $\pm$ SD of three independent experiments.

(B) Proliferation assay in NB4 cells expressing NTC or two independent UBE2E3-targeting shRNAs (sh UBE2E3 #10 and #21). Data are presented as mean $\pm$ SD of three independent experiments.

(C) Colony-forming assays in OCI-AML2 (left) and NB4 (right) cells expressing NTC or two independent UBE2E3-targeting shRNAs. Colonies were scored 10–14 days after plating in methylcellulose. Bars represent mean $\pm$ SD of three biological replicates; both shRNAs reduced colony formation relative to NTC ($P < 0.01$).

(D) Colony-forming assays in cells expressing NTC or UBE2E3-targeting shRNAs (TEX, sh#10 and sh#21; 8227, sh#21). Bars represent mean $\pm$ SD.

(E) Summary of GSEA (clusterProfiler) performed on OCI-AML2 RNA-seq following UBE2E3 depletion (Left panel). Positive NES (red) indicate enrichment of differentiation- and immune-associated programs

(monocyte-like, LSC⁻/non-stem, interferon- α response, genes down-regulated in LSC, glycolysis); negative NES (blue) indicate depletion of progenitor- and proliferation-associated programs (GMP-like, proliferative genes, MYC targets, E2F targets). FDR-adjusted q values are indicated; individual enrichment plots are shown in Supplementary Figure S4. The right panel shows the same analysis as a dot plot across the full set of AML cell-state signatures, with dot colour indicating NES and dot size the enrichment score.

(F) Leukemic engraftment of 8227 cells expressing NTC or shUBE2E3 in NS-GF mice; human GFP+CD45⁺ cells were quantified in bone marrow at the experimental endpoint. Each dot represents one animal; bars indicate mean $\pm$ SD; P=0.0068.

(G) Engraftment of primary AML cells transduced ex vivo with NTC or shUBE2E3 and transplanted into NSG mice; left, primary transplant (P = 0.002); right, secondary transplant (P = 0.001). Human engraftment was quantified as CD33⁺/CD45⁺GFP⁺ cells. Each dot represents one animal; bars indicate mean $\pm$ SD.

(H) Model summarizing the consequences of UBE2E3 depletion in AML: impaired leukemic growth, clonogenicity and leukemia-initiating activity, accompanied by a transcriptional shift from stem-like toward differentiation-associated states.

Abbreviations: AML, acute myeloid leukemia; FDR, false discovery rate; GMP, granulocyte-monocyte progenitor; GSEA, gene-set enrichment analysis; LSC, leukemia stem cell; NES, normalized enrichment score; NTC, non-targeting control.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTableS3UBE2E3BioID.xlsx](#)
- [SupplementaryExperimentalProceduresLeukemiaV03.docx](#)
- [SupplementaryTableS4UBE2E3proteomics.xlsx](#)
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